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The Effect of Heparinization upon Vascular Healing

FELIX BACIGALUPO, M.D.; ERWIN SIMANDL, M.D.; SHIVAJI B. BHONSLAY, M.D., and RALPH A. DETERLING Jr., M.D., New York

With the increasing application of arterial grafts and thrombendarterectomy for the treatment of occlusive arterial disease, the number of patients in whom the use of anticoagulant drugs might be considered beneficial in the postoperative period has increased. The action of these drugs in altering the clotting mechanism so that there is a reduced tendency for clot formation in diseased or injured blood vessels or at vascular anastomoses has been well recognized. The use of heparin and the prothrombin-depressing drugs has been established in the treatment of myocardial infarction, venous thrombosis, and peripheral arterial thromboembolism.[10-13,22,29,34,55,60,65,70-72] Ever since Murray[44,45,47] reported satisfactory results with the administration of heparin in association with blood vessel surgery there has been a general acceptance of the value of this agent for irrigating the open lumen of a blood vessel during the performance of an anastomosis, for the irrigation of catheters left in blood vessels, for instillation into blood vessels adjacent to occluding instruments, and for the irrigation of arterial or venous grafts.[6,16,24,41,70]

Strangely enough, the proper role of systemic anticoagulation in the period following the implantation of a vessel replacement for arterial occlusive disease has never been clearly defined; nor has the optimum time of initiating such a program or the most satisfactory method of administering heparin been properly established. The studies being reported had as their purpose the clarification of some of the factors involved in the answers to these questions. Among the factors investigated were the vehicles suitable for the injection of heparin, their mode and time of action, and optimal site of deposition, particularly as related to a continuous course of anticoagulation therapy in dogs over a period of 10 days. After the development of a completely satisfactory technique of long-term heparinization in the experimental animal, the study was directed to the effect on vascular healing by anticoagulating doses of heparin administered before, during, and after the performance of an aortic anastomosis.

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From the Department of Surgery, College of Physicians and Surgeons, Columbia University, and the Surgical Service of Presbyterian Hospital; Fellow of the New York Heart Association (Dr. Simandl).

Materials and Method

Heparin.—This mucopolysaccharide has been studied extensively, biologically and chemically, and a tentative formula has been proposed.[1,2,5,7,24,28,46,53,66,68] However, the precise nature of the naturally occurring substance has not been completely elaborated, and there are some doubts as to

whether it actually is a single chemical compound.[28,53,57,66] It is generally believed, however, that heparin produces its anticoagulating effect by interaction with certain substances and enzymes which affect fluidity and coagulability of circulating blood. Recent investigations in vitro[7] have demonstrated that heparin and its co-factor, which exist in plasma as well as in serum, combine to form a compound, known as heparin co-factor complex. This combination activates factor V and an accelerator factor, thus inhibiting the conversion of prothrombin to thrombin, but without exerting any direct action on prothrombin. It is also presumed that the same heparin co-factor complex inactivates thrombin as well as thromboplastin.[7] The resultant diminished coagulability of the blood is generally measured by the time interval necessary for the formation of a clot in freshly obtained whole blood in vitro. The venous clotting time (V. C. T.), which refers to the time required for clot formation in freshly drawn venous blood, is the usual clinical test employed to demonstrate the anticoagulation action of heparin.[16,27,28,32,42,43,47,63]

Clinical usage has favored the aqueous solution of heparin, obtained commercially in varying concentrations. Processes of purification in recent years have made this form suitable for deep subcutaneous administration[2,10,12,16,22,25,27,42] where relatively slow absorption is desired, as well as intramuscular injection[12,13,16,18,27,42,53,54,57] for more rapid effect, and, finally, intravenous administration[2,11,22,27,29,42,52,53,58] for almost immediate action. Although originally it was believed by some that, in order to be completely effective therapeutically, heparin had to be administered continuously by means of an intravenous infusion over a 24-hour period,[12,13,44-46] it was subsequently demonstrated that intermittent dosage by any of the routes described could achieve satisfactory results.[10-12,16,28,29,53,57,60] Current clinical usage has favored the deep subcutaneous injection of aqueous heparin solution at intervals of three, four, or six hours.[3,10,12,13,18] A daily dose of 200 to 300 mg. will generally serve to prolong the venous clotting time to about 20 minutes in the average adult human being.

Aqueous heparin solutions have also been administered continuously or intermittently into a vein or artery to maintain regional anticoagulation.[6,15,21,23,40,48,52,69] Certain difficulties and disadvantages inherent either in repeated puncture of a vessel or the continued presence of a catheter in a vessel adjacent to a critical area have led to this method becoming less popular in the last year or so. The primary advantage in this technique was in the establishment of the adequate anticoagulant state regionally without prolongation of the systemic venous clotting time. Without any accurate method of measuring the heparin effect at the local site, however, the exact degree of heparinization had to be assumed. A trial of sublingual administration[36] has not proved to be very efficient.

In addition to varying the site of deposition and type of administration in order to alter the rate of absorption of heparin, a diminished rate of absorption has been observed when the compound is administered intramuscularly in special media, such as gelatin and dextrose, with or without vasoconstricting drugs.[3, 12, 16, 26-28, 36, 37,42,43,59,65] Since the preliminary report in 1944 on the use of prolonged acting heparin by Loewe and Rosenblatt,[37] the media have been greatly improved. Because of the depot effect of the slowly absorbed menstruum containing the heparin, a therapeutic level may be maintained by a single dose over a period of between 12 and 48 hours. In general, this form of heparin has been more irritating to the tissues.

Significant variations in the individual response to heparin, administered in any form, have been observed clinically.[11-14,19,42,53] The response to heparin is diminished in the immediate postoperative period, at which time susceptibility to thrombosis is increased. This diminished response is also observed in certain disease states, particularly advanced

arteriosclerosis. Whereas older people are less reactive to heparin, young patients are very susceptible to its action. In addition, patients in shock or those suffering from hepatic disease may be very reactive to heparin.[12,13] A heparin tolerance test has been developed by De Takats [12,13] for titration of the compound in patients who might have an abnormal response. In general, however, the determination of venous clotting times just prior to the first few doses of heparin can permit the establishment of a satisfactory schedule of administration. Allergic reactions to heparin have occasionally been observed but are for the most part very mild.[8,10,11,16,53]

Experiments.—A total of 21 adult mongrel dogs weighing from 8.0 to 16.5 kg. were used in this study. Several determinations of the venous clotting time were made preoperatively, employing the Lee and White technique with uncoated chemically clean glass tubes.[2,10,25,32,42,48,57] A standard operative procedure was subsequently performed in all animals. The abdominal cavity was entered through a midline incision, and the lower segment of the abdominal aorta was mobilized and divided between Potts ductus clamps at a level about 2.5 cm. proximal to the trifurcation. The cut ends were then rinsed with isotonic saline solution and an end-to-end anastomosis performed by continuous suture, with use of 00000 braided nonabsorbable surgical (silk) sutures.* Following the release of aortic clamps, extreme care was exercised in achieving complete hemostasis at the anastomosis and in the entire operative area. This was of particular importance in certain animals to which heparin was administered prior to closure of the abdominal wound. The technique of heparinization was varied so that five different groups were studied.

Group I: Four dogs weighing from 10.0 to 16.5 kg. had a control venous clotting time between three and five minutes. Six hours after operation a dose of 10 mg. per kilogram body weight of heparin sodium solution in gelatin and dextrose (Depo-Heparin†) was injected intramuscularly. Satisfactory anticoagulation was achieved by the subsequent intramuscular injection of Depo-heparin in a dose of 10 mg. per kilogram body weight twice daily during a total period of 10 days for each animal.

Group II: Four dogs weighing from 8.0 to 14.8 kg. had preoperative venous clotting times ranging between two and three minutes. Immediately after closure of the skin incision, Depo-heparin, 5 mg. per kilogram body weight, was administered intramuscularly. Venous clotting time determined 3 to 6 hours subsequently and ranged between 8 and 29 minutes. Depo-heparin in a dose of 10 mg. per kilogram body weight was then administered again intramuscularly and subsequently twice daily for a period of 10 days.

Group III: Five dogs weighing from 9.5 to 13.2 kg. had a preoperative venous clotting time of three to six minutes. Immediately upon the completion of the aortic anastomosis, aqueous heparin in a dosage of 2.5 mg. per kilogram body weight was injected intravenously. A close observation of the anastomosis and operative field was maintained for 20 minutes. No blood loss occurred from the anastomosis except a brief insignificant ooze at the time when blood flow was reestablished following the anastomosis. There was minor oozing from the skin edges observed at the time of wound closure. This was satisfactorily controlled by meticulous hemostasis and firm wound closure. At the completion of the operation, venous clotting time ranged between 18 and more than 60 minutes. Three to four hours after operation, the venous clotting time ranged between 18 and 22 minutes. At this time the first dose of Depo-heparin, 10 mg. per kilogram of body weight, was administered intramuscularly and continued twice daily for 10 days.

Group IV: Four dogs with body weights ranging from 9.5 to 9.9 kg. had preoperative venous clotting times of three to six minutes. Aqueous heparin, 2.5 mg. per kilogram body weight, was injected into the abdominal aorta from 3 to 10 minutes prior to the application of the Potts ductus clamps. After reestablishment of blood flow, there was a persistent blood loss from the needle holes of the anastomosis during a period of 10 to 15 minutes in all animals. In some instances more superficial individual sutures were applied for hemostasis. Clotting time, determined in one animal at the time of the anastomosis, was found to be greater than 60 minutes in blood drawn from the jugular vein. Once control of blood loss was achieved, the suture line appeared satisfactory during the subsequent 20 minutes of observation period. Venous clotting time at the time of the closure of the abdominal incision was from 12 to more than 60 minutes. The venous clotting time 3 to 5 hours following operation, at which time the first dose of Depo-Heparin, 10 mg. per kilogram body weight was administered, was 12 to 24 minutes. The Depo-heparin was administered in this group twice daily for a period of 10 days.

* Supplied by J. A. Deknatel & Son, Inc., Queens Village, N. Y.

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Group V: Four dogs ranging from 9.6 to 11.5 kg. body weight had preoperative venous clotting times of one to four minutes. Aqueous heparin, 2.5 mg. per kilogram body weight, was injected intravenously 20 to 25 minutes prior to the time of aortic anastomosis. With the application of a meticulous operative technique, no increase of bleeding was observed during the period of mobilization of the aorta. At the time the anastomosis was performed venous clotting times were found to be from 35 to more than 60 minutes. The latter levels were observed in three animals. In all of these animals there was a prolonged leakage from the suture line, primarily from the needle holes. In most instances additional sutures were required to control all bleeding. Subsequently the suture line appeared satisfactory for 20 minutes of observation. In this group also there was an increase in bleeding from the skin edges which was controlled by hemostatic measures and firm wound closure with a continuous suture. The venous clotting time 3 to 5 hours postoperatively was 12 to 14 minutes, and at this time Depo-heparin, 10 mg. per kilogram body weight, was administered intramuscularly and twice daily subsequently for a period of 10 days.

The activity of the animals was not restricted following operation; they were allowed complete freedom in large metabolism cages, with an exercise period of at least an hour daily in a large room. Penicillin in a dose of 100,000 units was administered intramuscularly daily for five days. The animals were maintained on a standard kennel diet, without supplements. The abdominal wound and femoral pulses were examined daily. The period of observation following operation ranged up to 12 weeks, by which time adequate healing of the aortic anastomoses had been observed in a control series of dogs. At the time of autopsy special attention was given to the abdominal wound, retroperitoneal region, and the aortic anastomosis. A search was made for evidence of hematoma, inflammatory reaction, or recognizable abnormalities in healing processes. The entire abdominal aorta was excised and in some instances tested for bursting strength of the anastomosis by the injection of saline under pressure into an occluded length of aorta containing the anastomosis. The lumen of the aorta was inspected carefully for evidence of thrombi, and, finally, microscopic sections were made of the region of the anastomosis, by the use of hematoxylin-and-eosin as well as trichrome stains.

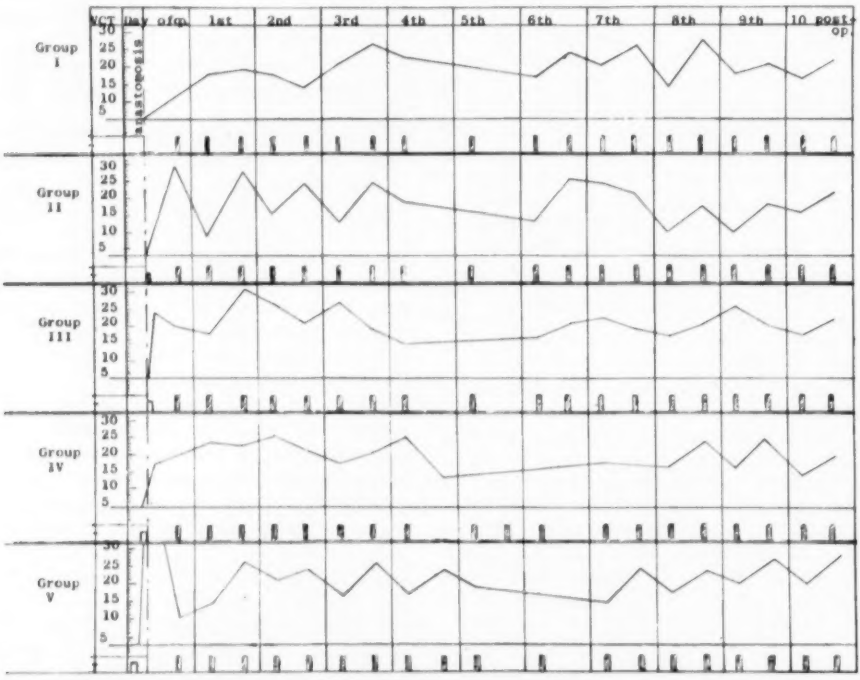


Fig. 1.—Average values of the postoperative venous clotting time for each group of dogs during period of heparinization. Open bars, regular heparin, 2.5 mg/kg.; shaded bars, Depo-heparin, 10 mg/kg.

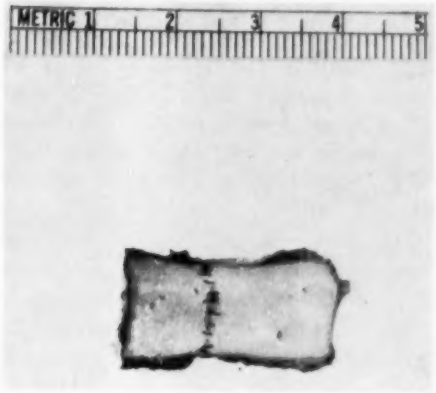


Fig. 2A.—Anastomosis of abdominal aorta eight weeks after operation. Intramuscular Depo-heparin was begun six hours after wound closure (Group I). There is firm union and smooth endothelization of the suture line.

Fig. 2B.—Suture line of abdominal aorta seven weeks after operation. Aqueous heparin was administered intravenously immediately after completion of the anastomosis (Group III). Heparinization was continued with intramuscular Depo-heparin. Healing appeared completely normal.

Results

Daily observation of the 21 animals during the postoperative period revealed strong femoral pulses in all instances. Five deaths from pneumonia occurred, three of which were in the first week and two in the second week postoperatively. In one animal an intestinal hemorrhage occurred on the second postoperative day. This persisted throughout a two-week period, at which time the animal died. It is of interest that the venous clotting time in this animal during the 10-day period of heparinization did not vary significantly from that obtained in the other animals without hemorrhagic complications. The remaining 16 dogs were observed for longer periods of time, up to 12 weeks, and behaved normally during this time. Minor oozing of blood from the skin incision was observed in four animals between the third and fourth postoperative days. It never lasted longer than two days nor was blood loss significant. All skin incisions appeared firmly healed at the time heparinization was stopped. The venous clotting time was maintained well above normal levels during the entire period of 10 days (Fig. 1).

The 16 animals without complications were killed between the 2d and 12th weeks.

Fig. 2C.—Suture line of abdominal aorta two weeks after operation. Aqueous heparin was injected into the aorta a few minutes before the anastomosis was begun (Group IV). Heparinization was maintained by intramuscular Depo-heparin. Healing had progressed normally, with complete endothelization.

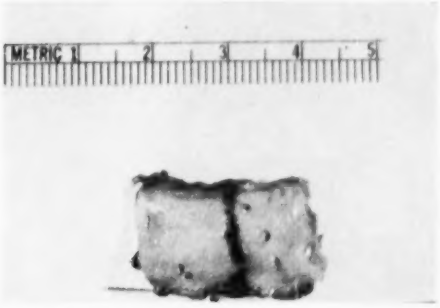
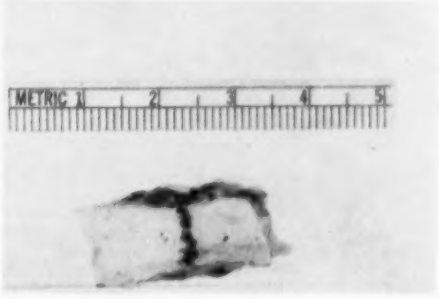


Fig. 2D.—Suture line of abdominal aorta three weeks after operation. Aqueous heparin was administered intravenously 20 minutes before the anastomosis was begun (Group V). Heparinization was continued with Depo-heparin. Healing was entirely satisfactory. No hematoma was present.



The gross appearance of the aortic anastomosis was excellent in the entire group of 21 animals. Externally, there was no evidence of hematoma, and internally there was no thrombus. The suture line was well endothelized in the specimens from all groups of animals (Fig. 2A, 2B, 2C, and 2D). The anastomosis resisted intraluminal pressures of 350 mm. of mercury at four weeks in specimens selected from Groups III, IV, and V.

Fig. 3.—Photomicrograph of anastomosis of abdominal aorta eight weeks after operation, hematoxylin-and-eosin stain; × 100. Satisfactory healing has occurred. Intramuscular administration of Depo-heparin was begun at the time of wound closure (Group II).

The microscopic appearance of the aortic anastomosis did not differ significantly from that of control specimens of comparable age (Figs. 3; 4A, 4B, 5A, 5B, 6A, and 6B). In three dogs dying during the latter part of the 1st week, there was complete endothelization. In specimens examined from the 2d to 12th week, there was a normal degree of fibroblastic activity leading to fibrous union, even in dogs from Groups IV and V, in which heparin had been administered prior to the anastomosis. In a few animals of the latter groups, there was microscopic evidence of minor hematomata in the outer layers of the adventitia (Fig. 6A and 6B). In these

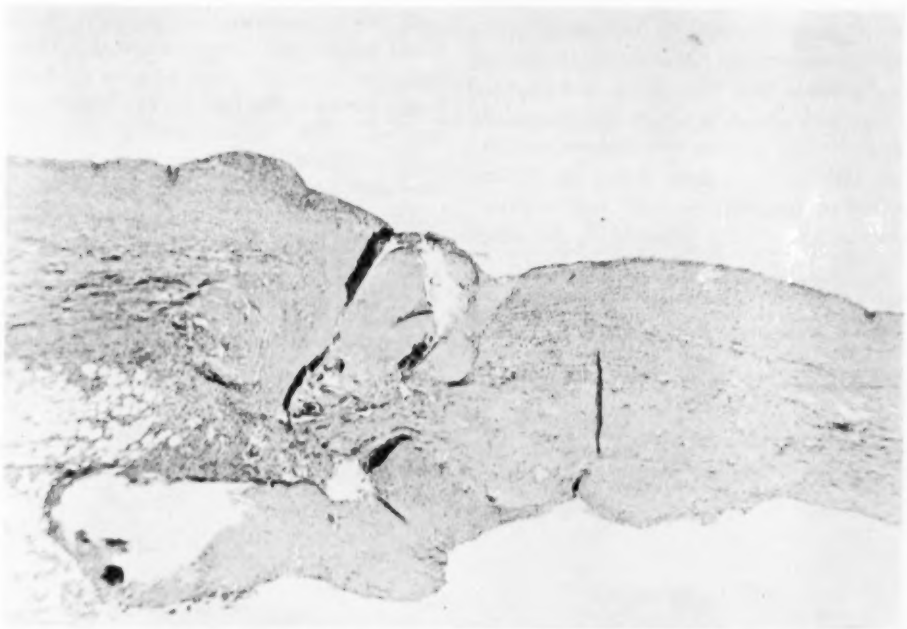


Fig. 4A.—Photomicrograph of anastomosis of abdominal aorta of dog from Group III, which died one week after operation. There is no evidence of hematoma or inflammatory reaction. Endothelization is complete, despite artefacts present in section. Hematoxylin-and-eosin stain; × 100.

Fig. 4B.—The same tissue treated by trichrome stain, demonstrating normal healing in process; × 100.

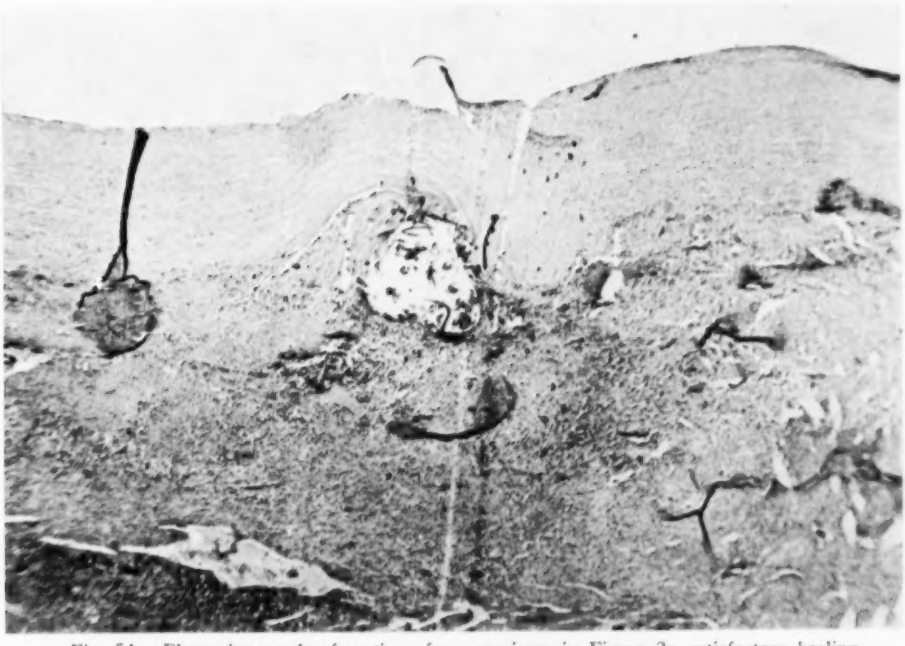


Fig. 5A.—Photomicrograph of sections from specimen in Figure 2c, satisfactory healing. No hematoma was present. Hematoxylin-and-eosin stain; × 100.

Fig. 5B.—The same tissue treated by trichrome stain; × 100.

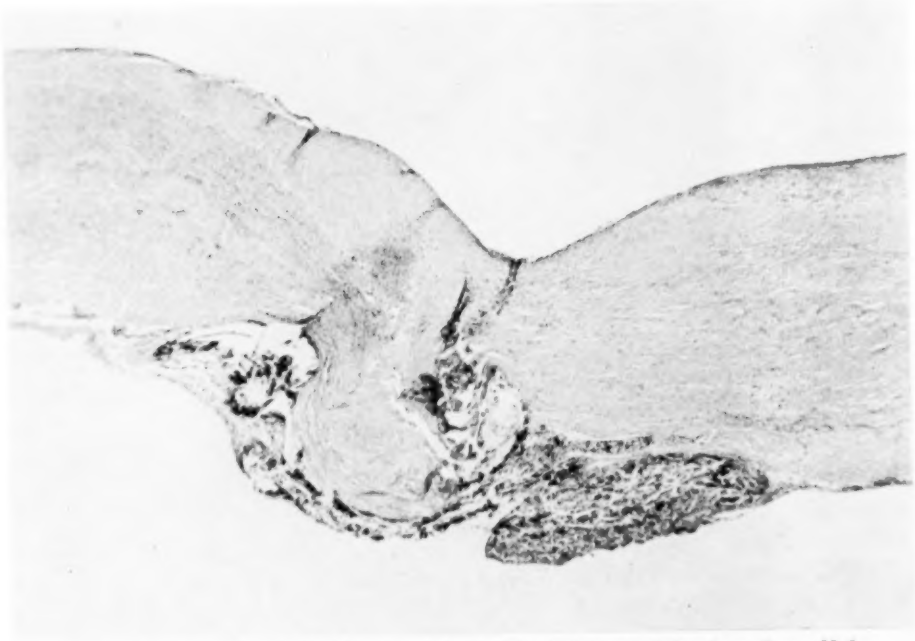


Fig. 6A.—Photomicrograph of anastomosis of abdominal aorta of dog from Group V five weeks after operation. Endothelization is complete, and firm healing has occurred. A small organizing hematoma is present in the adventitial zone; × 100.

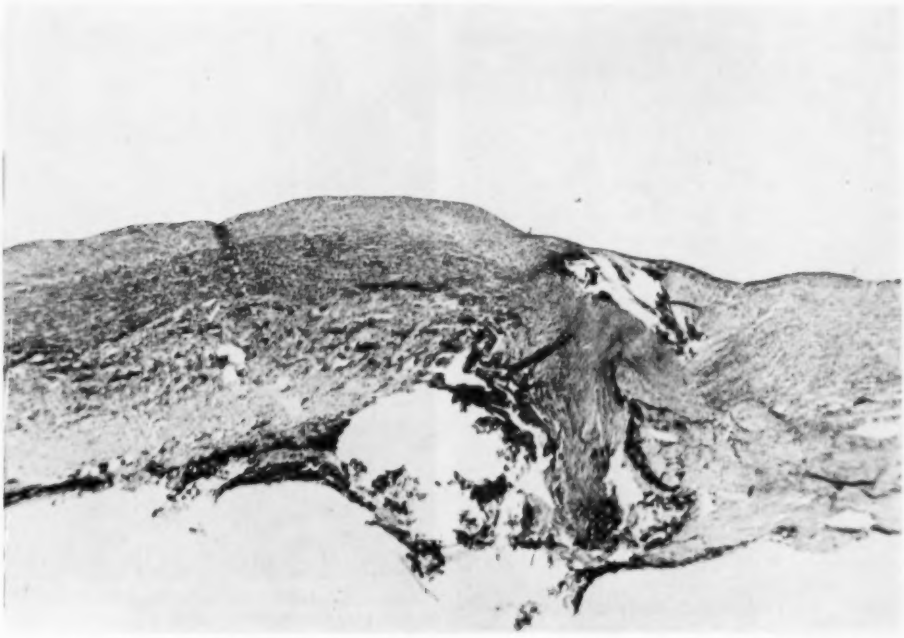


Fig. 6B.—A different section from the same specimen has been treated by trichrome stain to show satisfactory fibrous union; × 100.

animals, additional sutures had been applied to control persistent bleeding at the anastomosis. In certain sections, small granulomata were present about the silk strands of suture material, but these were observed in control specimens as well. This reaction is believed to result from irritation produced by a preparation of polyethylene glycols (Carbowax) commonly employed in the finishing of silk suture material.

Clinical Material

Subsequent to our experimental demonstration that vascular healing was not altered significantly in the presence of a prolongation of the venous clotting time into the therapeutic range, six patients were selected for a course of heparinization begun immediately following the reestablishment of blood flow through by-pass grafts inserted for the treatment of segmental arteriosclerotic occlusion of the superficial femoral artery. The decision to use anticoagulant therapy was based on the presence of moderate or advanced arteriosclerotic degeneration of the artery adjacent to the occluded segment, as well as the difficulty in performing technically satisfactory anastomoses. Because of atheromatous or calcific plaques at the site of anastomosis in some instances, a partial thrombendarterectomy had to be performed in order to make possible the insertion of a graft. The use of anticoagulation in association with the use of homologous arterial grafts in peripheral arteries has been the exception rather than the rule in our clinical experience (R. A. D.). The risk of bleeding associated with anticoagulation was accepted in our cases but was not considered to be greater than that associated with any type of major general surgery. In none of our six patients was there evidence of leakage from the anastomoses nor of significant hematoma in the operative area or wound. In all patients, the venous clotting time was kept in a therapeutic range from the time of operation until heparin was stopped. In general, after heparin was administered in-

itially, it was given by deep subcutaneous injection, in a dosage of 40 to 75 mg. every four to six hours. On the second to fourth day following operation, bishydroxycoumarin (Dicumarol) was given orally to some patients, in a dose of 300 mg., followed by 150 to 200 mg. the next day. Thereafter, the dose was adjusted according to daily estimations of the prothrombin time of venous blood. The use of heparin was discontinued in these patients after the first week. In other patients, heparin alone was used for the entire course of treatment. Complete and satisfactory function of the graft persisted in all patients except one (Case 1).

Case 1.—A 62-year-old white man was admitted to Presbyterian Hospital on Jan. 9, 1956, because of intermittent claudication of the left calf of four months' duration. Examination revealed no pulses in either leg distal to that in the femoral artery at the groin. A bilateral femoral arteriogram revealed a 9 cm. segmental occlusion in the region of the adductor canal in each superficial femoral artery. A more extensive collateral circulation was present on the right.

On Jan. 12, 1956, the left femoral artery was exposed and a quick-frozen homologous arterial graft was then inserted as a by-pass, with end-to-side anastomoses just above and below the occluded segment. Upon removal of occluding cotton tapes from the femoral artery, no blood flow was detected in the graft. The upper anastomosis was opened and fresh clot was extracted from the graft. When the anastomosis was completed and blood flow was reestablished, a very poor pulse was present in the distal portion of the graft. More clot was removed through a small arteriotomy in the femoral artery just proximal to the distal anastomosis, but the pulse was not greatly improved. At the time of wound closure, 35 mg. of heparin was injected intravenously and 50 mg. of heparin was given every six hours subcutaneously during the next week. The venous clotting time ranged from 13 to 30 minutes, immediately prior to a dose of heparin. Because of coolness of the left foot, and absence of pedal pulses, an arteriogram was performed on the sixth day. The graft was occluded, without involvement of the patient's artery, or collateral channels, by fresh clot (Fig 7).

On Jan. 19, 1956, the thrombosed homograft was excised. A new frozen arterial homograft was implanted as a by-pass, proximally as before, but inserted into the popliteal artery 3 cm. below the previous distal anastomosis. When blood flow was established, the graft pulsated well and pedal pulses were felt. Immediately, 40 mg. of heparin was injected intra-arterially above the graft, and the venous clotting time was 12 minutes at the end of the operation. Intermittent doses of heparin at 6-hour intervals were continued for 10 days without incident. Pedal pulses remained strong at the time when the patient was last examined, six months after operation.

Fig. 7.—Arteriogram revealing complete occlusion of homologous arterial graft used to by-pass a 9 cm. occlusion of the superficial femoral artery. Collateral circulation has not been disturbed by the insertion of the graft nor by its subsequent thrombosis.

Comment.—The failure of function of the homograft developed prior to the institution of heparinization. It is believed that anticoagulation prevented propagation of the fresh thrombus into the distal arterial segment. Following the second operation it is believed that anticoagulation contributed to continued success during the period of healing, especially in view of the markedly calcified and atheromatous vessel. It is of interest that the patient now notes claudication in his right calf. Operation on this side is planned for the future.

Case 2.—A 58-year-old white man was seen in the hospital on Nov. 15, 1955, because of claudication of the right calf of three years' duration. Examination revealed a femoral pulse only at the groin on the right. An arteriogram demonstrated

Fig. 8A.—Arteriogram revealing almost complete occlusion in midportion of right superficial femoral artery, as well as multiple atheromata. Calcific plaques are visible in the artery of the opposite leg, in which satisfactory pulses were present.

Fig. 8B.—Occlusion of the superficial femoral artery has occurred immediately below the distal anastomosis of a Dacron fabric by-pass graft to the superficial femoral artery. This is approximately 5 cm. below the original site of occlusion.

Fig. 8C.—Satisfactory restitution of blood flow in the extremity followed the insertion of an arterial homograft to by-pass the segmental occlusion which developed distal to the Dacron fabric graft.

a partial occlusion of the right superficial femoral artery, in the midportion of the vessel (Fig. 8A).

Operation was performed on Dec. 12, 1955. The superficial femoral artery contained numerous calcific plaques, and no pulse could be palpated below the site of obstruction. A specially woven tubular graft of polyethylene terephthalate (Dacron) taffeta with curved ends‡ was implanted, bypassing the occluded segment. Heparin and saline solution was injected by means of a small polyethylene catheter into the distal artery at the time of the implantation, as is regularly performed. Transient obstruction to the passage of the catheter down the artery was noted, however, approximately 2 cm. distal to the lower site of implantation of the prosthesis. At the completion of the operation, heparinization was begun because of the absence of pedal pulses. Forty milligrams was injected at intervals of 6 hours, maintaining the venous clotting time between 12 and 30 minutes. Two weeks later, arteriography

‡ Developed by Meadox Weaving Co. in conjunction with Dr. Ormand Julian, Dr. Ralph Deterling, Jr., Mr. Titus Haffa, and Mr. William Liebig. An article entitled "Synthetic Fabric Arterial Prostheses Woven To Specification: Experimental and Clinical Use" is to be published in *Surgery*.

was performed (Fig. 8B). The Dacron fabric graft was patent, but the femoral artery was occluded distal to the lower anastomosis for a distance of 6.5 cm. Heparinization was stopped on Dec. 30 because of mild epigastric symptoms thought to be related to a previous duodenal ulcer.

On Jan. 16, 1956, the artery was again exposed. The fabric replacement was pulsatile and was invested by a firm coating of fibrous tissue. An 8 cm. frozen homograft was implanted, by-passing the new segmental occlusion. The upper anastomosis was placed in the arterial wall opposite the lower anastomosis of the fabric graft. Heparinization was again begun at the time of wound closure, 35 mg. being administered at intervals of 6 hours, for 10 days. Arteriogram on Jan. 7 demonstrated patency of both grafts (Fig. 8C). Strong pedal pulses were palpable when the patient was examined almost six months later.

Comment.—It was thought that the segmental occlusion occurring distal to the implanted Dacron prosthesis resulted from trauma to the vessel at the time the polyethylene catheter was introduced. In all likelihood a small plaque was loosened which later dissected and occluded the artery. It is believed that heparinization contributed to the continued patency of the fabric graft emptying into a short patent segment of artery. It is questionable whether anticoagulation was indicated following the second operation.

CASE 3.—A 70-year-old white man was admitted Dec. 6, 1955, with intermittent claudication in the left calf of two months' duration as well as cyanotic discoloration of the third toe of the left foot. Whereas pulses could be felt throughout the right leg, on the left only the femoral pulse was palpable. An arteriogram revealed a segmental occlusion of the middle third of the left superficial femoral artery.

On Dec. 13, 1955, exploration revealed the occlusion, 4 cm. below the femoral arterial bifurcation. Since a suitable graft was not available, thrombendarterectomy was performed, with removal of thrombus and thickened intima from a 28 cm. segment of superficial femoral artery. This segment was irrigated with heparin and saline solution, and, after closure of an arteriotomy at either end of the segment, pulsation could be detected in the popliteal artery, with reestablishment of blood flow. However, peripheral pulsations could not be detected in the foot. Beginning immediately after completion of the operation, heparin was administered subcutaneously in a dose of 50 mg. and repeated every six hours for three days; then anticoagulation therapy was continued with bishydroxycoumarin. The prothrombin time ranged between 28 and 45 seconds. On Dec. 18 an arteriogram revealed occlusion of the left superficial femoral artery. Since the circulation in the third toe had not improved, left lumbar sympathectomy as well as nerve crush of the superficial and deep peroneal nerves was performed. A slow continued progression of the gangrene of the toe led to reoperation on the left leg Jan. 5, 1956. A 45 cm. frozen arterial homograft was implanted with end-to-side technique, thus bypassing the occluded superficial femoral artery. Thirty-five milligrams of heparin was administered intravenously during closure, and heparinization was continued for one week. After operation, pedal pulses could be felt and circulation in the nongangrenous portion of the third toe returned to normal. Pulses could still be felt six months after operation.

Comment.—The failure of anticoagulation to prevent complete occlusion of the artery subjected to thrombendarterectomy would appear to be related to impaired outflow, as indicated by the subsequent appearance of peripheral pulses following the use of a graft. In addition, relatively little prolongation of clotting times was achieved until the effect of bishydroxycoumarin was evidenced. In our clinical experience, heparin has appeared to be a more effective anticoagulant drug, but it must be used in an adequate dosage. The success of the homograft bypass was indeed welcome and unexpected in this aged man with incipient gangrene. There is reason to believe, because of the advanced and extensive arteriosclerosis in the extremity, that heparinization following the use of the graft contributed to continued patency during the healing period.

CASE 4.—A 64-year-old white man was admitted March 5 because of intermittent claudication of the left leg. A multisaccular abdominal aortic aneurysm had been excised in April, 1955. The abdominal aorta below the renal vessels as well as the common iliac arteries and right external iliac and common femoral arteries were excised, with a bifurcation graft of nylon taffeta fabric being used for replacement. At the time of admission in 1956, femoral pulses were palpable bilaterally but no pulses were present distally on the left. An arteriogram revealed a segmental occlusion of the left superficial femoral artery. On April 17, 1956, an arterial homograft was implanted end-to-side, by-passing the occluded segment. Fifty milligrams of heparin was injected intravenously at the time

of wound closure, and intermittent subcutaneous heparinization was continued until May 4, 1956, maintaining venous clotting time at 17 to 36 minutes. During the latter period of heparinization, bishydroxycoumarin was also administered because of evidence of a deep phlebitis. At the time of discharge from the hospital, May 6, 1956, pedal pulses were palpable in the left foot.

Comment.—Of interest in this patient is the continued function of the left limb of the nylon bifurcation despite occlusion distally of the superficial femoral artery. Of further interest is development of phlebitis which followed operative manipulation of the left femoral artery and vein. Phlebitis has been reported as a common complication of such surgery, but in our experience it has occurred in less than 20% of cases.

CASE 5.—A 64-year-old white physician was admitted Aug. 9, 1954, because of intermittent claudication of the right calf of 10 months' duration. Pulses were absent distal to the right femoral pulse at the groin. Arteriogram revealed a 4 cm. occlusion of the distal portion of the right superficial femoral artery. Following a bilateral lumbar sympathectomy, the occluded segment was excised and a 14 cm. autogenous vein graft of saphenous vein was implanted. Subsequent occlusion of the vein graft was confirmed by arteriogram.

The patient was readmitted one year later because of increasing claudication of the right leg and the recent development of claudication in the left calf. No pulses could be felt distal to the common femoral arteries. Bilateral arteriogram performed Aug. 5, 1955, demonstrated again the occlusion of the vein graft on the right as well as an 8 cm. obstruction in the lower portion of the left superficial femoral artery. A frozen arterial homograft was implanted on the left, bypassing the obstructed segment. Excellent pulsations were felt in the dorsalis pedis artery after surgery.

On Aug. 15, 1955, the right femoral artery was explored and a markedly contracted thrombosed vein graft was identified. A 28 cm. arterial homograft, which had been preserved in electrolyte solution at 4 C was implanted as a by-pass. Since no definite pulses were felt in the foot immediately following surgery, although the skin was of good color and temperature, heparin, 50 mg. every 6 hours for 8 days, was administered to maintain the venous clotting time between 12 and 27 minutes. At the time of discharge excellent pulses were felt in the left foot but not in the right.

Comment.—In this man the partial failure of the homograft on the right could be explained in part by some compromise of the outflow tract following thrombosis of the vein graft. It is believed that heparinization helped maintain whatever success was achieved, and the physician can now walk as much as his occupation requires without claudication.

CASE 6.—A 59-year-old white woman was admitted March 6, 1956, complaining of bilateral intermittent claudication of the calf of six years' duration. Arteriography confirmed the clinical impression that there was a very extensive occlusion of both superficial femoral arteries. A seriogram was necessary to demonstrate patency of the popliteal vessel on the right side.

On May 21, 1956, a 30 cm. frozen arterial homograft was inserted into the right superficial femoral artery, by-passing the occlusion. A thrombendarterectomy of the superior portion of the common femoral artery was necessary in order to effect adequate anastomosis. Heparin was administered in a dose of 50 mg. subcutaneously at the completion of the anastomoses and administered at six-hour intervals thereafter. Palpable pedal pulses persisted after operation. After one week anticoagulation therapy was continued by bishydroxycoumarin.

On May 29, 1956, a frozen femoral homograft of similar length was implanted as a by-pass in the left superficial femoral artery. At the time of surgery the prothrombin time was 20 seconds. Absolutely no bleeding problems were encountered during operation. Bishydroxycoumarin therapy was continued during the postoperative period. No pulse could be felt in the foot on the left side subsequent to operation, but the skin was pink and warm. Ambulation was accomplished without claudication.

Comment.—This patient had extremely poor arteries, with calcification and marked intimal thickening even in the patent segments. The upper anastomosis on the right side was technically unsatisfactory despite a thrombendarterectomy. The continued presence of palpable pedal pulses was indeed reassuring. The partial success on the left side was believed due to small-vessel occlusion in the lower leg, and the maintenance of adequate circulation was believed due in part to anticoagulation.

These experiences indicate some of the types of cases in which anticoagulation was considered worth the risk of complications from bleeding. In no instance was there any evidence of hematoma or fresh bleeding,

and in all patients the wounds healed without incident. Nevertheless, it is important to mention briefly one additional patient who had serious difficulties related to postoperative bleeding.

This was a 62-year-old white man who had complete arteriosclerotic thrombotic occlusion of the abdominal aorta distal to the renal arteries as well as iliac vessels and common femoral arteries. A thrombendarterectomy was performed with some difficulty because of the extreme degeneration of the vessels, and the left external iliac artery was considerably thinned as a result of the procedure. Anticoagulation with heparin was begun immediately postoperatively, but bleeding subsequently occurred from a small rupture of the anterior surface of the left iliac artery. It was of interest that satisfactory healing had occurred in a rather long aortotomy incision as well as in six additional incisions in the common iliac, external iliac, and common femoral arteries. It was thought that this complication developed more because of mechanical thinning of the vessel at the time of thrombendarterectomy than from a failure of healing because of anticoagulation.

Comment

Justification for the use of anticoagulation immediately following any major surgery should of course depend on the strength of the indication for its use, acceptance of the effectiveness of such therapy, and acceptance of the risks associated with treatment. With regard to vascular surgery, the indications for use might be the presence of technical faults in a vascular anastomosis, marked arteriosclerotic disease in the region of an anastomosis, the use of very long grafts or extensive thrombendarterectomy in the treatment of occlusive disease, and kinking or torsion of a graft or vessel—all of which conditions favor the development of thrombus. Proof of the effectiveness of anticoagulation therapy with heparin is not within the scope of this report.

There are recognizable risks involved in the use of anticoagulation therapy, whether or not surgery has been performed. Among the most important dangers from the point of view of the surgeon are hemorrhage and impairment of wound healing. Evidence of minor bleeding has been noted in most reported series of patients treated with heparin and/or a prothrombin-depressing drug. The incidence of epistaxis, minor hematomata, mild hematuria, or rectal bleeding has fortunately not been great. In general, this is readily controlled by cessation of therapy and local measures, as indicated. However, one must also admit to instances of major hemorrhage and even death resulting from anticoagulation therapy.

In an early report on the use of heparin and bishydroxycoumarin, Barker[4] noted 3.1% of minor bleeding and 1.9% of major hemorrhage among 1686 medical, surgical, and gynecological patients treated at the Mayo Clinic. In 1950, Nichol[49] presented the results of a questionnaire inquiring about the complications associated with anticoagulation therapy. From among 15,500 patients treated with heparin and/or bishydroxycoumarin by 136 physicians, there were 4% minor bleeding, 2% major bleeding, and 0.18% deaths related to the treatment. These were medical as well as surgical patients, 90% of whom received bishydroxycoumarin only. Walden et al.[65] evaluated complications of long-term anticoagulant therapy of myocardial infarction and concluded that more patients died without therapy—even with the risks of treatment included. It appears that most complications have been associated with long-term therapy by the prothrombin-depressing drugs. Likewise, bishydroxycoumarin was the only or the predominant drug being used in patients dying of bleeding believed to have been produced by anticoagulation therapy, in the series reported by Duff and Shull,[17] Duryea,[18] and Lilly and Lee.[33]

Prophylactic anticoagulation as protection against thromboembolism following a general surgical procedure has long been employed by some physicians for older patients

undergoing certain types of operations.[11,15,23,34,44-46] Statistics have suggested that phlebitis occurs most often after surgery involving pelvic organs, lower abdominal viscera, and abdominal wall. With the early use of bishydroxycoumarin, it was customary to administer the first dose orally on the third morning following surgery. Subsequently, when heparin was used for an earlier effect, the first dose was generally given the day following operation. Less often was anticoagulation begun in the period 4 to 12 hours postoperatively.[10,11,28,29,45,47,50,52,58,60,62] Murray, who had employed general heparinization at the time of a vascular surgical procedure, emphasized that, although this therapy could be considered safe once hemostasis had been achieved, there might be delayed bleeding resulting from an increasing blood pressure as the patient emerged from the anesthetic state. Consequently, he advocated beginning the administration of heparin no earlier than four hours after operation. On the other hand, it is evident, as Shumacker[59] and others have pointed out, that thrombosis is most apt to occur in the immediate postoperative period. This is especially true in vascular surgery, and complete thrombosis of a graft or artery may be observed within an hour or two of the time of operation. Even if heparin may not prevent functional failure of a graft in some instances, it may well prevent propagation of the thrombosis. It was the aim of regional heparinization to alter the clotting mechanism immediately following a vascular injury or the production of an anastomosis without the risk of general anticoagulation.[6,15,23,47,69] However, vascular injury occurred at the site of the administration, and uncertainty existed as to the actual degree of heparinization in the desired area unless the general venous clotting time was elevated. Although more than 100 patients were treated with regional heparinization via plastic catheter in major artery or vein at Presbyterian Hospital during the years 1950 to 1954,[21] there has been infrequent if any use of this technique since then. When general anticoagulation has been employed, a delay of four to eight hours has usually been traditional following operation. Our experiments supported the belief that, if a good indication for general anticoagulation actually exists, administration of heparin can begin immediately after operations involving peripheral arteries.

If surgery is performed during a state of adequate heparinization, there is significant bleeding from capillaries and small vessels. However, major surgery has been carried out on patients during anticoagulation by bishydroxycoumarin without significant complications. Blood loss during mitral commissurotomy was measured by Storm and Tybjerg[62] in patients being given anticoagulation therapy with bishydroxycoumarin and in a control group with normal prothrombin times. The differences were not significant. Muellertz and Storm[48] reported results of operation upon patients who had been given bishydroxycoumarin and noted no significant bleeding related to therapy. Littman[35] and associates reported satisfactory experience in performing major operations after anticoagulation therapy with bishydroxycoumarin. In Case 6 of our report, no bleeding tendencies were observed during insertion of a femoral by-pass graft while the prothrombin time was increased.

Aside from the consideration of bleeding, the question has been raised as to whether heparin inhibits healing significantly.[9,30,31,39,41] Surely this effect would be of paramount importance to the vascular surgeon. Admittedly, depression of mitotic activity has been demonstrated in vitro, as has delay of proliferation of cells in tissue culture.[20,51,73] Heparin has not halted cell growth, however, in such experiments.[73] Certain investigators have presented experimental evidence suggesting that there is interference with healing of skin wounds as a result of the effect of heparin or bishydroxycoumarin.[9,39,41] On the other hand, no alteration in wound healing has been observed by De Takats,[12,13] Sandblom,[55,56] Laufman et al.,[30,31] Littman et al.,[35] and others, provided

meticulous hemostasis and careful approximation of skin edges were carried out. A large hematoma may interfere with healing of any wound. Tensile strength of a healing vascular wound is not diminished by heparinization, according to our studies and those by Laufman and Heller.[80] Furthermore, we found no evidence of impaired healing of the abdominal incisions of dogs nor of the skin incisions of the seven patients subjected to immediate full heparinization.

We would caution against the use of any anticoagulant drugs in patients with hepatic or renal disease, blood dyscrasias, or ulcerated areas, or in those with evidence of gastrointestinal or renal bleeding. Indeed, such therapy should not be employed in any patient without sufficient indications. At the present time, we would hesitate to recommend immediate use of heparin in patients with abdominal or thoracic vascular procedures or in cases with synthetic vascular replacements, although we have done so without difficulties. Major bleeding into the abdominal or thoracic cavities may be more difficult to recognize and is generally more serious in respect to management than is bleeding in the wound of an extremity. A greater danger of bleeding from a porous synthetic replacement may be theoretical, since all loss of blood through such a graft should have stopped before administration of heparin. Since functional results with grafts have been least satisfactory in the smaller arteries, it is expected that the widest use of immediate postoperative anticoagulation will be in patients with occlusive peripheral vascular disease.

Summary

Suture anastomoses of the abdominal aorta were performed in 21 dogs subjected to heparinization. There were variations in mode of administration and in the time relationship to the performance of the anastomosis. In no instance was there postoperative bleeding from the suture line, and study of the aorta during intervals up to 12 weeks after operation revealed no impairment of tensile strength or abnormality in the healing of the anastomosis. No hematoma developed, and wound healing was satisfactory. In a selected series of six patients with a bypass graft of the superficial femoral artery, heparinization was begun immediately after reestablishment of blood flow through the graft. No complications referable to anticoagulation were observed.

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DISCUSSION

ON PAPERS BY DRS. WARREN AND BELKO* AND BACIGALUPO, SIMANDL, BHONSLAY, AND DETERLING.

DR. JOHN H. OLWIN, Chicago: I would like to discuss Dr. Warren's paper and congratulate him on a very nice study. I would like to make two points.

I think in dealing with either heparin or any of the prothrombin depressants we must understand that we are dealing with drugs which affect not only one factor, but many factors, both coagulation and anticoagulation, and in using thromboplastin in any study we are dealing with a very critical factor in many instances.

Recently in our laboratory we studied six different thromboplastin preparations, four of them being available commercially, two of which we prepared in our own laboratory. [Slide] Observing them in the so-called one-stage test which is used routinely in most laboratories, using the same plasma, at the same time, and as nearly as possible the same technique, varying only the thromboplastin—at whatever the level of prothrombin as measured by the two-stage test—we found a variation of up to 90% in the prothrombin levels by

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the one-stage test. Is it little wonder that there is such a wide difference of opinion on the use of anticoagulants, particularly prothrombin depressants?

Until the present time we have considered that anticoagulants have dealt largely with the preventing of the extension of a clot already formed or to its prevention prophylactically. However, recently Dr. Helen Wright, in England, has given us the first evidence that these may not be the only effects that we are achieving by giving these anticoagulants. A third effect is the promotion of the resolution of the clot. In rabbits she produced thrombin by injecting sodium morrhuate and thrombin into segments of the femoral arteries. You can see [Slide] arteriographically that there is a complete block of the femoral artery in these animals and you can see the occluding thrombus here microscopically. In the control animals receiving no drug, the block remains after four months. In animals receiving ethyl biscoumacetate (Tromexan) the block disappeared in two to four weeks. This is the original picture, this is the picture after two to four weeks, and this is the vessel microscopically. There was complete recanalization by both roentgenologic and microscopic evidence.

Dr. Frank H. Leeds, San Francsico: I would like to discuss Dr. Deterling's paper briefly. My associate, Dr. Norman Freeman, and I have been intensely interested in the immediate use of heparin in persons subjected to arterial surgery and over the past five years in operations on 102 patients, we have employed heparin in 70, beginning immediately at the time of operation. Our technique for administering heparin has been through the placement of a small polyethylene tube into the vessel above the anastomotic area and using a continuous drip of heparin solution. At the time of leaving the operating room, the venous clotting time (Lee-White method) of all of these patients has been more than 20 minutes. Heparin has been continued for about four days. Only one patient succumbed to hemorrhage in this group of 70. In our third case, the heparin drip was inadvertently speeded and the venous clotting time rose to 120 minutes. This emphasizes the need for careful and continuous attention to such patients in the postoperative period.

We believe it is feasible to give heparin immediately following anastomoses in arteries, but like the authors we have considered it of great importance to check carefully our suture lines before completing the operation. We wait as long as 30 minutes to be sure there is no bleeding and add extra sutures if necessary. At the present time we have gradually reduced the indications for the use of early heparin and now restrict it to patients who have obvious gangrene in the toes, those who have extensive distal arterial obliteration, or to those who for some technical reason have an unsatisfactory anastomosis. We believe that in selected cases the early use of heparin can increase the percentage of salvage by arterial surgery and permit operation on certain patients in whom otherwise operative procedures would be contraindicated.

In 20 patients in whom we have used either Orlon or crimped nylon grafts, we have had serious bleeding through the graft itself, and we believe now that if we must use a synthetic graft the use of an anticoagulant drug is probably contraindicated within the first 12 hours, at least.

Dr. Edward A. Edwards, Boston: A brief comment regarding Dr. Warren's topic. I can recall two patients with extensive venous thrombosis, who were doing well under heparin therapy, who suffered a disastrous advance of the thrombosis when a change was made to bishydroxycoumarin (Dicumarol). This occurred with a prothrombin level well below 10%. The thrombosis was again well controlled when heparin was reinstituted.

We feel it is dangerous to make a change when a critical process is being well controlled by heparin. If long-term therapy seems desirable in such patients, it is perhaps safer to change the anticoagulant only after heparin has been in use for two or three weeks and best if the patient is already ambulatory.

Dr. Warren, Boston: I want to thank both Dr. Olwin and Dr. Edwards for their discussion and to reemphasize that these methods are not 100%. These observations were made using a tissue thromboplastin. There are two other elements to thromboplastin, namely, plasma and platelet thromboplastin. There is no intimation, therefore, that the test exactly mimics the thrombotic process in vivo. I am also aware of the fact that the one-stage test has certain disadvantages.

I would like to say that in the use of heparin it is important, if we are going to interpret any of these things clinically, that we keep an anticoagulant effect all around the clock and that we do not whistle in the dark by giving a little shot every 12 hours.

Dr. Deterling: I would like to thank Dr. Leeds. I did not mention in the presentation our work with regional heparinization which was begun after the lead of Dr. Freeman and others. I believe there were about 150 patients at Presbyterian Hospital in whom regional heparinization was performed, a great number of them being cases with splenorenal shunts.

In these, the heparin drip was begun fairly soon after the operation, but not on the operating table, as I recall. I carried it out in some arterial cases

and at times got into technical difficulty. In our technique a continuous infusion was administered above the anastomotic site by means of a fine indwelling catheter. In one instance I recall the patient rolled over on the connecting tubing and effectively stopped all administration of heparin and everything clotted nicely.

One of the advantages claimed for the technique was that one did not have to achieve generalized anticoagulation. However, if the value obtained in the venous blood from the arm was not evaluated, you had no idea what was going on at the anastomotic site. Generally, there was a little bit too much guess work involved, and we ultimately had to gauge our dose by elevation of the VCT of peripheral blood—in other words, general anticoagulation.

In the laboratory we had put some fine catheters into the inferior vena cava of dogs, and we found clot formation on the catheter between the site of the introduction of the catheter and its tip. Although the blood beyond it was all right, when the catheter was withdrawn there was a clot adherent to the wall where it had been introduced—a potential source for progressive thrombosis or embolus.

Late hemorrhage through cloth grafts is a danger, and we have observed it in several instances. Reoperation was required in one patient not receiving anticoagulant therapy. I share in the reluctance to employ such drugs when using synthetic replacements, particularly with a porous type.

Experiences with Ivalon (Polyvinyl Formalinized) Sponge Prostheses for Vascular Replacements

WILLIAM B. AYERS, M.D.; JOHN J. CINCOTTI, M.D., and MARVIN L. GLIEDMAN, M.D., Brooklyn

Until approximately one year ago, we had been fairly well satisfied with lyophilized homografts for use in vascular replacements for central artery defects. However, because of involved difficulties in procurement of homografts in our area (particularly regarding distal arteries) plus the failure on occasion of venous autografts,[1] the late suture line disruption in some homografts in our own and others' experience * and occasional aneurysm formation in homografts reported by others,[2] we undertook a search for other and more ideal prostheses where the problem of supply would not be ever-present.

Our present solution to the problem is Ivalon (polyvinyl formalinized) sponge, as described by Shumway and his associates.[9] This sponge is strong, resilient, elastic when wet, and, when washed free of chemical contaminants, inert in tissue.[4,9] Ingrowth of fibrous tissues and capillaries into implanted sponge occurs in a regular "noninflammatory" fashion so that there is no true foreign-body reaction and scar formation.

Hufnagel's [7] criteria for successful vascular substitutes seem to us to be fulfilled exceedingly well, namely, biologic inertness, adequate resistance to stresses and strains in tissues and the deteriorating effects of body chemicals, resistance to clotting, extreme smoothness of the tube lining, and imperviousness to "weeping and sifting" of blood. The material sutures easily and holds the sutures well, is easily tailored without raveling, tearing, or splitting.

We have had aluminum stents manufactured to our specifications (Fig. 1) so that the prosthetics can be made of a size which has almost universal applicability. The Ivalon as purchased must be washed very thoroughly to free it of a preservative the manufacturer puts in. The sponge is then allowed to dry and can be easily cut into strips with a meat slicer or a band-saw.

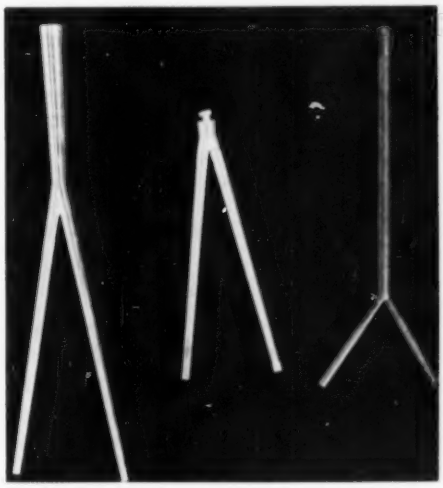

Fig. 1.—Stents used for fabrication of plastic sponge tubes, one at left being the presently used modification.

Rewetting the sponge strips restores their elasticity and allows them to be wrapped in a spiral fashion around the stent, overlapping each successive turn by three-fourths of the width of the previous turn.

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Associate Professor of Surgery, State University of New York College of Medicine, New York City (Dr. Ayers), and Chief of Surgical Service, Veterans Administration Hospital (Dr. Cincotti).

* Case study under present investigation.

The whole plastic-wrapped stent is then covered with a wrapping of wet 2-in. roller bandage or wide cotton tape, this outer wrapping being applied as tightly as possible by manual tension over the plastic wrappings. This presses the plastic tightly against the smooth stent and insures a glass-smooth lining to the prosthesis. Our wrapped stent is then autoclaved for 15 minutes.

We have used both end-to-end and end-to-side anastomoses. It had been noted that plastic cloth prostheses could be used with difficulty or not at all in making end-to-side anastomoses, but we have found Ivalon tubes perfectly adaptable for this type of anastomosis. All diameters of blood vessels, including the aorta, common iliac, external iliac, femoral, popliteal, and subclavian (third portion), have been so treated. The suturing details are simple over-and-over sutures with 0000 or 00000 nonabsorbable surgical (silk) sutures interrupted twice around the circumference of the suture line. Technical ease of suturing is greatly aided by the fact that the tubes maintain their cylindrical shape and do not collapse when wet, as do the plastic cloth tubes.

We have used all lengths of tubing, from 2.5 cm. to 45 cm. in length. The length chosen for a prosthesis is done by allowing the tube to lie in the tissue planes without tension, in the case of the lower limb, in neutral extended position. After the prosthesis is sutured in place, passive flexion of the limb will usually demonstrate whether there is undue torsion or buckling, and this can be corrected if necessary. The tubes have been put across flexion creases including the groin and the knee without buckling.

We have found that immediate use of anticoagulants given systemically upon release of occluding clamps at the end of the surgical procedure is desirable. This is in addition to flushing of the distal occluded arterial tree with moderately large amounts of a dilute solution of heparin (10 mg. per 100 cc.), done during the procedure from time to time. After this, anticoagulation is continued for 10 days.

We have also thought it necessary to recommend that where the tubes cross flexion creases that the limb involved be immobilized for 10 days by plaster casting. Antibiotic therapy is used routinely in all patients, as the host suture lines, as always, are susceptible to break-down subsequent to a development of infection.

The following group of cases were selected for Ivalon sponge tube prosthetic replacement, as they represent a fairly broad cross section of degenerative arterial disease.

1. Aneurysms

A. Aortic

CASE 1.—*Bifurcation graft*

This 68-year-old white man was admitted for low back pain and abdominal pain and hypertension of eight months' duration. Studies revealed an aneurysm of the abdominal aorta beginning just below the renal arteries and extending down to include the bifurcation of the aorta and right common iliac artery. The an-

Fig. 2 (Case 1).—Postoperative arteriograms showing shunt in place five months postoperatively.

eurysm was resected and replaced by an Ivalon sponge prostheses fabricated over a brass stent made to order at the time of operation. The whole process from time of ordering the prosthesis to its availability was approximately one hour. On implanting the prosthesis an error in judgment as to the length of the aortic limb was made, necessitating resection of a portion of this limb and making an additional Ivalon-to-Ivalon anastomosis necessary. Upon release of the occluding clamps, no bleeding or leakage at the Ivalon-to-Ivalon suture line was seen, and only a small leak at the host artery prosthetic anastomosis was evident. No postoperative anticoagulants were used in this patient. He made an uneventful recovery and is doing well at the present time, 24 months postoperatively, with good distal pulses.

CASE 2.—*Straight aortic graft*

This 70-year-old white man entered the hospital because of abdominal pain associated with an enlarging tender mass in the left side of the abdomen which on exploration proved to be a large sacular aneurysm of the aorta showing signs of early rupture. This was resected from just below the renal arteries down to but not including the bifurcation of the aorta, and a straight Ivalon prosthetic tube was implanted. The patient's postoperative course was uneventful. Three months following this he was admitted for heart failure on the basis of coronary insufficiency; he died four weeks later. At autopsy, the prosthesis was intact and functioning. Figure 3 demonstrates the graft in situ at time of autopsy.

Fig. 3 (Case 2).—Close-up of patient. Postmortem specimen showing smooth intimal-like lining to prosthesis and endotheliolization of suture lines. This at time of death at three months. Note peeling away of graft from surrounding tissue and lack of cicatrical fixation.

CASE 3.—*Bifurcation graft, end-to-side anastomosis (ruptured aneurysm)*

This 68-year-old white man entered the hospital Nov. 22, 1955, as an emergency, complaining of severe epigastric and low back pain and pain in the left groin of four days' duration. Studies indicated a large calcific mass in the lower abdomen consistent with an aortic aneurysm. There was evidence of an old myocardial infarction. On the day of admission, the patient was virtually anuric, and surgery was delayed for this reason. We felt that, since in our experience patients with ruptured aneurysms which have been resected have died anuric from renal failure, there was little to be gained in resecting the aneurysm unless the patient demonstrated the ability to make urine. Specific therapy directed at the anuria produced an actual diuresis, and exploration was then done. A ruptured aortic aneurysm was found and removed with resection of the aorta from the renal arteries down to and including the bifurcation and common iliac arteries. Because of extreme calcification of the right iliac artery, an end-to-side anastomosis was done on this side and an end-to-end type on the left side. Subsequently, the patient did well and has continued to do so. An aortogram taken four months postoperatively demonstrating the patency of the prosthesis is shown.

CASE 4.—*Bifurcation graft*

This 59-year-old white man entered the hospital on Sept. 26, 1955, because of urinary difficulties, intrinsic asthma, and chronic confusional state secondary to arteriosclerosis. An abdominal aortic aneurysm was discovered incidentally and proved on aortography. After clearing of the urinary difficulties and alleviation of the asthma, the aortic aneurysm was removed and an Ivalon prosthesis implanted. The prosthesis included the bifurcation of the aorta, and distal anastomoses was done end-to-end to both common iliac arteries. Postoperatively, the right leg showed evidence of mild ischemia, apparently secondary to an embolus from a sclerotic plaque at the area of resection. This responded very well to epidural block with procaine. The leg subsequently became warm and functioning, and he had no further diffi-

Fig. 4 (Case 4).—Arteriogram taken five months postoperatively, showing Ivalon prosthesis in place, an end-to-side anastomosis on the right, and an end-to-end anastomosis on the left common iliac artery.

culties with it. The remainder of his postoperative course was uneventful, and an aortogram taken five months postoperatively showed good functioning of the prosthesis (Fig. 4).

Case 5.—*Straight graft—postoperative thrombosis*

A 33-year-old Italian man entered the hospital because of an enlarging pulsating mass in the left supraclavicular fossa of several months' duration. Examination showed an aneurysm of the left subclavian artery, the etiology being a tight anterior scalene muscle band stretching across the artery to a cervical rib, producing a poststenotic dilatation and aneurysm of the artery. The aneurysm was resected, and an Ivalon prosthesis implanted approximately 6 cm. in length, the process necessitating resection of the outer two-thirds of the clavicle. Postoperatively, the patient did well until the fourth postoperative day, when an episode of severe epigastric pain associated with generalized vasospasm occurred. Thereafter the pulse at the left wrist disappeared and has not returned to present. However, there has been no disability in the left arm and no reduction in exercise tolerance or other evidence of ischemia there. The patient continues to have episodic, epigastric, and precordial pains similar to the one which occurred in the hospital, which are now thought to be due to diaphragmatic flutter. Episodes of vasospasm evidenced by whitening of the hands and generalized pallor still occur, associated with the epigastric pain. No anticoagulants were used.

Case 6.—A 32-year-old Negro man entered the hospital because of pain and disability of the left leg of one month's duration. Previously he had had a ligation of a popliteal aneurysm of the right leg done elsewhere. At the present admission here, a popliteal aneurysm in the left leg was found, and excision done with replacement by an Ivalon prosthesis. Postoperatively, the patient was placed on anticoagulant therapy, beginning with heparin at the end of this surgical procedure and continuing with phenindione (Hedulin) postoperatively. He is doing well, with distal pulses present in the leg operated on, and it was noted that flexion at the knee produced no decrease in these pulses.

Three other abdominal aortic aneurysms have been grafted (by other associated surgeons); two of these patients died in the immediate postoperative period, one of renal failure and the other of acute coronary artery occlusion. One had a patent graft at autopsy; in the second case permission for autopsy was refused.

2. Arterial Thrombo-Obliterative Disease of the Extremities

A. Femoral

Case 1.—*Shunt graft*

A 68-year-old white man entered the hospital because of rest pain and intermittent claudication in the right leg of many months' duration. The arteriograms demonstrated segmental occlusion of the right superficial femoral artery (run-off of anterior and post-tibial arteries not seen). A bypass shunt measuring 14 in. (35 cm.) in length extending from the common femoral to the popliteal artery in its midportion was implanted with an end-to-side anastomosis at each end. Postoperatively, he was not placed on anticoagulant therapy but otherwise did well except for a wound infection which developed in the upper end of the popliteal incision. This was explored after it had been treated for several weeks without subsidence, and a few silk sutures were found which apparently went down to the area of the Ivalon prosthesis. The graft did not appear to pulsate. However, a needle aspiration of it revealed that it contained free-flowing bright red blood. At the present time, the patient's claudication and rest pain has completely disappeared, so that he can walk vigorously for many blocks without having to

stop. An arteriogram was attempted, and filling of the graft was not seen. Clinical evidence would indicate that the graft may be open, although distal run-off is obviously poor, as both posterior tibial and dorsalis pedis pulses did not return, even immediately postoperatively. This points up the necessity both of administering anticoagulants postoperatively, and also, where there is doubt of main channel patency distally, of doing an open arteriogram at the time of exploration of the popliteal artery.

CASE 2.—*Iliac (Shunt graft across flexion crease)*

A 67-year-old white man entered for severe rest pain and claudication and a superficial ulceration of the right foot. Examination revealed also that he had areas of superficial gangrene on the tips of all toes. Only a faint femoral pulse was obtainable on the right side and no pulses distal to this. Oscillometric examinations below this point were zero. Arteriograms showed a block of the right external iliac artery, and consequently a bypass shunt with Ivalon was done from the right common iliac artery down to the common femoral artery, running the graft beneath the inguinal ligament, the graft being 8 inches (20 cm). in length. Anticoagulants were used immediately postoperative—and continued for two weeks. On the third postoperative day, this patient developed a confusional state, climbed over his bed boards, and was found walking around the wards. After this, the confusional state rapidly cleared spontaneously, and since then he has been completely ambulatory. Distal pulses are present in the femoral and popliteal arteries and in the posterior tibial, which had not been present at all preoperatively. The distal gangrene on the tips of the toes is completely healed, as is the ulceration on the dorsum of the foot. All rest pain has completely disappeared, and the patient is doing well as far as his peripheral arterial system is concerned.

CASE 4.†—*Shunt graft*

A 77-year-old white woman entered for gangrene of the toes of the left foot. An arteriogram showed that the left femoral artery had a segmental block just above the origin of the popliteal with distal filling of the popliteal artery but not beyond this. A saphenous vein shunt graft was done, and postoperatively she received anticoagulants and the usual antibiotics. However, repeat arteriograms six weeks later showed that the shunt graft was thrombosed. Following this, an Ivalon shunt graft was inserted end-to-side from the common femoral artery down to the popliteal artery over a distance of 20 in. or 50 cm. This particular shunt graft bled profusely, because of poor fabrication and the fact that the Ivalon was too thin. After the second procedure, because of the bleeding in surgery, no anticoagulants were given. It was noted that no pulses developed postoperatively and the gangrene progressed, so that a midthigh amputation had to be done. Infection developed in and around the upper femoral vein shunt anastomosis, and eventually this had to be ligated to prevent hemorrhage. Examination of the amputated leg showed a thrombosis beginning at the host side of the end-to-side anastomosis in the popliteal artery, but no thrombus was actually present in the Ivalon tube itself (Fig. 5).

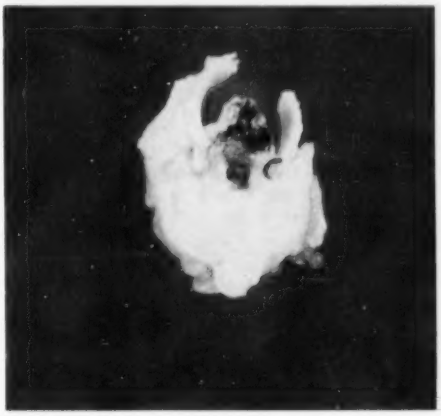

Fig. 5 (Case 4).—Cross section at end-to-side anastomosis of shunt to popliteal artery, demonstrating clot initiating at artery side of anastomosis, but lying free in the shunt attached to it.

This case represents one of poor selection with very poor run-off through the anterior and posterior tibial arteries. (Further examination and dissection showed that these vessels were completely occluded by arteriosclerosis.) An open femoral arteriogram would have saved a good deal of work and trouble for the patient.

CASE 5.—*Shunt graft*

An 80-year-old man developed gangrene of the left third toe, necessitating amputation. However, healing was slow. Arteriography showed a block in the lower superficial femoral artery. An Ivalon tube shunt graft was inserted from the common femoral artery down to the

† Dr. L. Brown, Meadow Brook Hospital, Hempstead, N. Y. performed the surgery.

popliteal artery. Postoperatively, the patient was given anticoagulants, and it was noted thereafter that both incisions in the thigh were oozing blood so that anticoagulation had to be stopped. These areas were explored, and a bleeding point in the upper anastomosis was found and sutured closed. No anticoagulation was done thereafter, but bleeding continued and reexploration again showed a bleeding point in the upper anastomosis which again was sutured. It was obvious at this time that some infection existed in this area. Reexploration was then done again and the anastomosis of the upper femoral artery was taken down; a new shunt was applied from the external iliac artery, extending beneath the inguinal ligament down to the old Ivalon tube below. The arteriotomy in the femoral artery was sutured closed. Postoperatively, it was obvious that his left leg was not receiving any blood. The left femoral arteriotomy began to bleed again, and on reexploration, the patient died during surgery. The examination at autopsy showed that there was a small clot attached to the new Ivalon shunt beneath the inguinal ligament; the remainder of the shunt graft, however, was completely free of clot. An infected wound was found in the femoral artery, and it was from this, of course, that he had been bleeding on unrepeated occasions. The reason for the clotting in the graft beneath the inguinal ligament is not clear in this case, inasmuch as a plaster spica had been applied and no flexion at the inguinal crease had occurred. The patient, of course, had not received anticoagulants since the first attempt at shunt grafting. This case we believe represents a failure due to infection in and around a suture line which repeated explorations and resuturing did nothing to help. In retrospect certainly the entire area should have been excised and an entirely new shunt or new graft been placed in the area of broken down arteriotomy.

3. Venous Transplants

Case 1.‡—A 60-year-old man was admitted to the hospital for resection of a squamous-cell carcinoma of the soft palate, with local invasion and metastasis to the neck. He had had a previous course of x-radiation therapy of 4700 r. to this lesion on the left neck without regression of the tumor. A resection of the primary lesion with a left radical neck dissection in continuity was done in Jan., 1956, with an uneventful postoperative course. On May 22, 1956, a right radical neck dissection was done because of appearance of nodes in this area. The right internal jugular vein was sacrificed, and this defect was replaced with an Ivalon sponge graft. Postoperatively, the patient has developed no edema of the face or neck, and his postoperative course has been otherwise uneventful. No anticoagulants were used. Postoperative phlebogram seems to indicate that the graft is occluded, however.

Case 2.—A 9-year-old white boy had had a splenectomy for so-called Banti's syndrome six years previously and massive bleeding from esophageal varices. A portacaval shunt was done utilizing an Ivalon tube graft to bridge a defect between the portal vein and the vena cava. The graft measured 2.25 cm. in length and 8 mm. in internal diameter. At the end of the procedure, the graft was obviously open and working, but no proof of this has been obtained at this time. No anticoagulants were used.

Case 3.—*Shunt graft*

A 56-year-old white woman had a long standing history of an arteriosclerotic ulcer of the right ankle. Lumbar aortograms showed evidence of occlusion of the external iliac artery near the inguinal ligament. A saphenous vein bypass shunt graft was done from the external iliac artery down to the common femoral artery near the profunda femoris. Postoperatively, very little change in the ulcer of the foot was noted. Repeat arteriograms showed that the vein shunt graft was thrombosed. Exploration of the popliteal artery at this point showed it to be thrombosed, but that there was a retrograde flow from the posterior tibial artery. A 58.5 cm. (23 in.) polyvinyl graft from the external iliac artery was then placed down to the posterior tibial artery with an end-to-side anastomosis at both ends. The patient was heparinized postoperatively, but control was not too adequate, so that at times the clotting time was over one hour. A large retroperitoneal hematoma developed and was evacuated. The ulcer of the foot and heel did not improve and frank gangrene eventuated after a period of two weeks. Consequently an above knee amputation was done. Examination of the amputated extremity showed that all of the main veins were thrombosed as well as the femoral artery and popliteal artery. However, although there was a thrombus in the Ivalon tube graft, actually this was thought to be a postoperative phenomenon by the Department of Pathology, inasmuch as there was no adherence of the

‡ From the Head & Neck Service, Kings County Hospital, Drs. Robert Freund and C. Pereyma.

clot to the shunt wall. Also, it was noted that the graft was probably too long, inasmuch as bending the knee produced a W-shaped kink in the polyvinyl formalinized sponge tube occluding the lumen.

This case represents one of poor selection, in that the distal run-off through the posterior tibial artery (which was the only one patent) was not sufficient to take care of the increased flow of blood down to it delivered by the shunt graft, and an open arteriogram would have demonstrated this and precluded grafting in the first place.

Comment

Examination of the failures have been most instructive, particularly since all human material was used. The findings correlate well with the known fate of sponge prostheses in animals.[4,8,9] There is laid down on the inner surface of the prosthesis a fibrinoid material about 0.5 mm. in thickness resembling nothing more or less than the intima of an artery. It can be stripped free from the surface of the Ivalon sponge tube. It is this which certainly prevents the thrombosis in the graft and, having been laid down over a suture line, probably prevents clotting there. However, we believe anticoagulation is necessary to prevent thrombosis at the suture lines until they are really well covered with endothelium. The interstices of the sponge are seen microscopically to be infiltrated with fibrous tissue and capillaries (Fig. 6) again as seen in experimental animals. It should be pointed out, as Grindlay has emphasized, that this infiltration is not cicatrical, and therefore the Ivalon is actually not tightly adhered to the surrounding tissues. Actually the surrounding tissues slide over it as they do any other layer of fibrous tissue, unless, of course, infection has been superimposed. But this lack of tissue reactivity certainly allows this material to be placed in flexion creases and in other areas where there is a good deal of torsion, strains, and stresses. The whole prosthesis is moderately stiffened and is not quite as elastic as time goes on, but it is not rigid. We should like to make the additional point concerning selection of cases that arteriograms, as we all know, can be extremely misleading as far as distal run-off is concerned, or patency and nonpatency of blood vessels. Consequently, on exploration of distal blood vessels, such as the popliteal, retrograde bleeding from the artery (Henle-Coenan phenomenon) has been taken heretofore to mean that distal run-off should be adequate. However, we believe now that this can be erroneous and that collaterals can give fairly brisk retrograde bleeding and mislead the surgeon into

Fig. 6.—Photomicrograph showing cross sections of Ivalon tubes which have been implanted for 10 days, demonstrating ingrowth of fibrous tissue, blood vessels, relative lack of inflammatory response. Technical difficulties have not allowed us to show the fibrinoid intimal lining which these grafts acquire.

thinking that distal main-channel run-off is adequate. As recommended above, open arteriograms should be done on the table at the time of exploration so that pictorial evidence of the main-channel run-off can be had. A shunt delivering a tremendous amount of new blood to an arterial tree which is all but occluded will cause a great deal of turbulence and has probably been responsible for clotting in some of our cases.

Summary

Cases are presented of arterial and venous replacement for various degenerative arterial diseases and for reestablishment of main critical venous channels, utilizing Ivalon (polyvinyl formalinized) sponge prosthesis. It will be noted in perusing the cases that causes of failure, with thrombotic occlusion of the prosthesis, have been due to poor case selection in two instances, in that the cases had poor main-channel run-off distally, as proved by examination of amputation specimens postoperatively. There have been two instances of late thrombosis in grafts across flexion creases (iliofemoral), one due to unknown cause in a dying man which never received any flexion, and the other secondary to poor main-channel run-off. Early thrombosis in another case (subclavian artery) may be explicable on suture line thrombosis due to severe vasospasm. Replacement of critical venous channels has not been successful with the possible exception of one case (portacaval shunt).

Types of anastomosis have included both end-to-end and end-to-side in varying sized arteries down to the posterior tibial. Both varieties of anastomosis have proved to be successful. The present plan of immediate postoperative use of anticoagulants has proved to have been safe, and we believe it is probably essential for a week to 10-day period until the suture line is endothelized, for it is this area which is the critical one as far as thrombosis is concerned. Long prostheses, over 25 cm. in length, are feasible and practical, the length apparently having no relation to success or failure. However, we realize that a long follow-up, of at least a year, is necessary for evaluation of the most distal shunt grafts.

Conclusions

Ivalon (polyvinyl formalinized) sponge tube prostheses have been successfully used to replace arteries of various sizes, by utilizing both end-to-end and end-to-side anastomoses. Replacement of venous channels is not recommended.

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DISCUSSION

ON PAPERS BY DRS. ROSENBERG, HENDERSON, DOUGLAS, LORD, AND GAUGHRAN*; DRS. AYERS, CINCOTTI, AND GLIEDMAN, AND DRS. KITTLE AND TAQUECHEL*

DR. WILLIAM E. NEVILLE, Cleveland: I enjoyed Dr. Ayers' paper. I should like to interject a word of caution in the use of the Ivalon sponge. A few years ago Dr. Clowes and I began using this experimentally. We implanted this material in a total of 25 dogs. I will have to admit that we made the grafts entirely different from the Minneapolis group. We fashioned the grafts out of blocks of Ivalon, using ordinary cork borer. I agree with everything Dr. Ayers said as to the ease of handling and suturing the material; it is wonderful, but following the

* These papers were published in the January, 1957, issue of THE ARCHIVES.

animals up to two years after operation we found that in only four instances had the grafts not dilated or become aneurysmal. The results, we felt, were so poor, that we decided not to use this clinically. There seems to be at the present time so many other prostheses available that it does not seem to us this type of material should be used for human grafts.

DR. EDWIN J. WYLIE, San Francisco: The last two discussers almost kept me in my seat, but not quite. We have used Ivalon in human operations for only one year. Our three-year follow-up may perhaps bring to light the difficulties just mentioned.

Eleven bifurcation prostheses of Ivalon have been implanted. Graft failures have developed in two. The first was due to an improperly fashioned stint which, by creating an irregularity in the lumen, we believed contributed to thrombosis of one of the iliac arms. The other prosthesis was made too thin. The graft dilated as soon as blood flow was established through it. Dilatation was followed by uncontrollable oozing of blood through the interstices. To control the bleeding an overlapping cylinder of Ivalon was sutured around the original graft. Seven days later the patient died from intra-abdominal bleeding due to leakage from the lower end of the cylinder.

After that experience we have increased the thickness of the Ivalon. There have been no other instances of aneurysmal dilatation. It now appears that a 15 mm. thickness of uncompressed Ivalon is adequate to prevent dilatation. Subsequent compression at the time of molding is done to make the inner lining smooth and to make the graft more suitable for suturing.

This slide shows the stint which was fashioned by our instrument maker. The joints at the point of bifurcation may be disassembled to release the graft. Its taper at the upper end allows the graft to be cut to fit the size of the proximal host aorta.

The next slide shows an Ivalon bifurcation prosthesis in place. To emphasize Dr. Ayers' comment about the ease of suture of this material, it was necessary in this graft to tailor the upper end of the aortic portion cutting from it a pie-shaped section. No bleeding appeared at the site of suture of Ivalon to Ivalon.

The last slide shows the postoperative aortogram from this patient. The graft has been encircled with a ring of catgut to which has been applied the silver clips which are here visible. Postoperative KUB x-rays are used to assess possible graft dilatation rather than aortography.

Our longest follow-up with the use of Ivalon prostheses has been eleven months. There have been no instances of graft dilatation. Aside from the two graft dilatations noted above and one death from coronary occlusion three months after operation, the results from this method have been satisfactory.

In the patient who died of coronary occlusion we were surprised to find in the section of the graft no evidence of fibrocytic infiltration as has been described by Dr. Grindley. I would like to ask Dr. Ayers if he had the opportunity to study microscopically his Ivalon prosthesis after implantation.

I did not go into the details of the fabrication of these prostheses sufficiently. I do know that if you use cork borer prostheses and don't compress it properly, you will get into trouble with it. We cut this material into strips four or five mm. in thickness, wet it, and then wrap the stents in an overlapping spiral manner so that each turn around the stent is overlapped by the subsequent turn by two thirds of its width. We then compress this with a very tightly bound roller bandage or wide cotton tape, which is also wet. This is then autoclaved. We have had no trouble with sifting or weeping of blood through the material.

With reference to the patient who died, I do not have slides to demonstrate it, but the manuscript has a photomicrograph demonstrating a section through this patient's protheses showing ingrowth of capillaries and fibrous connective tissue. There is no splitting of the sponge and the section is identical with those seen experimentally.

Therefore, I believe, if properly fabricated this material will be found to be extremely useful.

DR. SHIVAJI BHONSLAY, New York: I would like to make a few comments on some experimental work Dr. Deterling and I did three years ago, evaluating skin grafts as well as Ivalon sponge. Insofar as the Ivalon sponge is concerned, I think our experiences are similar to those of Dr. Neville. Special tubular Ivalon was made for us. All the slightly compressed tubes that were implanted in the thoracic aorta ruptured in four to thirteen days. Others in the abdominal aorta remained open for a period up to one year. Almost all of these were dilated and there was a tremendous amount of fibrous tissue surrounding the graft.

After this study we implanted into the thoracic aorta Ivalon grafts which had been greatly compressed. In this series there was dilation of the graft in about 60% of the dogs at the end of 18 months, and in the remainder

of the group up to two years there has been incidence of thrombosis of 35%.

We feel that so long as better substitutes are available, the use of Ivalon sponge as an arterial graft is not justified. We believe that at the present time perhaps the best substitute for peripheral arteries is the homograft.

Going back to the experimental work we have done with skin grafts, we implanted into the thoracic aorta of dogs a series of tubes fashioned from fresh autologous skin. All of the grafts made of split thickness skin ruptured up to a period of 35 days, whereas the ones made from whole skin remained intact. The thrombosis rate was 80% in these, however.

Surgical Treatment of Lymphedema of the Upper Extremities

GERALD H. PRATT, M.D., and ARTHUR A. LEVINE, M.D., New York

We have been interested in the surgical therapy of various types of lymphedema for the last 20 years and have operated on more than 150 patients with this disease. It is both epidemic and endemic. More recently we have described and discussed an operation for lymphedema of the lower extremities which, in most patients, has proved quite satisfactory.[1-4] Lymphedema of the upper extremity, because of its location, the obvious necessity for the use of the hands, and because of the extent of the physical and psychic damage this condition causes, poses a special surgical problem. Owing to the time factor, no history or details of previous therapy on lymphedema is included in this discussion.

Embryology

The lymph system originates, like the vascular system, by a transformation from venous endothelium into paired tubes or sacs which fuse into the jugular and iliac lymph channels from the jugular and iliac veins. These tubes early lose their vein connections. The unpaired lymphatics develop from the vena cava and mesonephric veins retroperitoneally to join and form the cisterna chyli. The lymph nodes arise from capillary plexus at the third month. The lymphocytes form lymph masses and nodules.

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Read before the Fourth Scientific Meeting of the North American Chapter of the International Society of Angiology, Chicago, June 9, 1956.

Physiology

The lymph system collects chyle in the intestines and transports it to the veins. It also collects lymph from other organs and the extremities. It also plays certain important roles.

Surgical Importance of the Lymphatic System

The adult lymph system plays a part in three surgically significant ways:

1. It is a localizer and to some extent a container of inflammation and malignancy.

2. After a certain period of time or saturation, it appears to overload like a full sponge and then becomes a transmitter for the dissemination of infection or malignancy.

3. An obstruction of the lymphatics, whether of congenital or acquired origin, often creates a surgical problem. The lymph collections secondarily overwork the correlative venous system and then the blocks result in massive and often disabling swelling. It is this latter condition with which this discussion is concerned.

Anatomy

The lymph system consists of lymph fluid, nodes, and vessels starting as capillaries and then becoming larger vessels. In the upper extremities there is a superficial and deep lymph system. The lymph vessels from the thumb and index finger and the dorsum of the hand join those draining the radial side of the forearm. These conduits then drain to the axilla. Those lymph channels from the third, fourth, and fifth fingers on the dorsal and flexor side drain to the axillary nodes. The superficial and

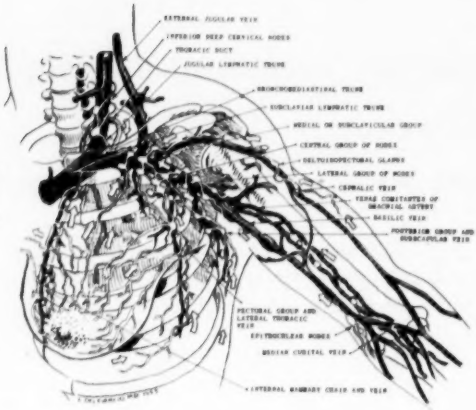


Fig. 1.—Anatomy of lymph drainage to the axillary area. Arrows indicate direction of drainage. (Pratt, from Christopher, F.: Textbook of Surgery, Lea & Febiger, 1956).

Fig. 2.—Lymphedema, congenital type, left arm. Note other lymphatic collections.

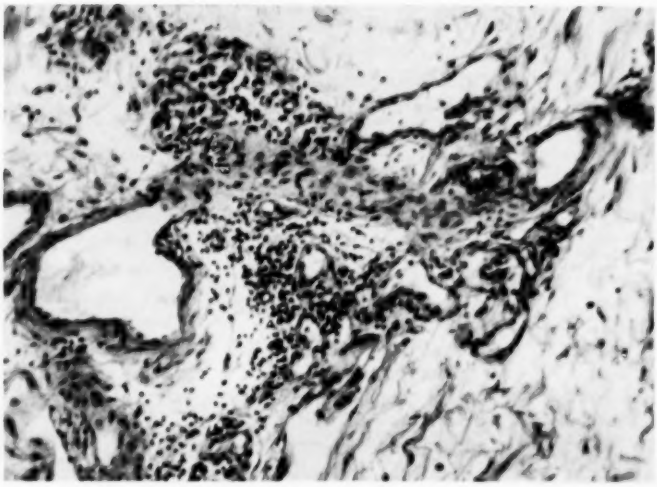


Fig. 3.—Lymph spaces and dilated vessels due to lymphedema. (Pratt, from Christopher, F.: Textbook of Surgery, Lea & Febiger, 1956.)

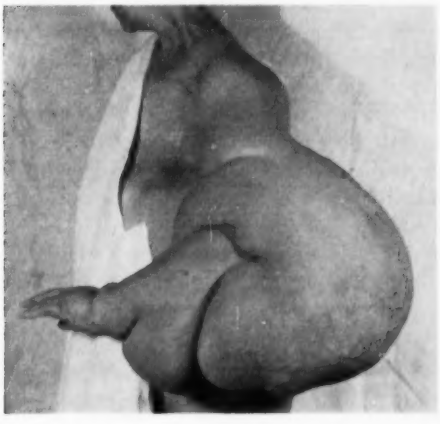
Fig. 4*A*.—Congenital lymphedema of the arm. Child aged five.

Fig. 4*B*.—Correction of lymphedema, arm stage

Fig. 4*C*.—Continuation lymphedema treatment to the hand (Fingers done as separate and final stage).

Fig. 5*A*.—Massive lymphedema following carcinoma of the breast and x-ray therapy. Patient's breast removed 10 years prior to operation for lymphedema.

Fig. 5*B*.—Postoperative pictures after treatment of lymphedema. Eighty pounds removed from the arm. Note deformity caused by excessive weight of arm. (Pratt, from Christopher, F.: Textbook of Surgery, Lea & Febiger, 1956.)



deep nodes are connected at the elbow area. The deep lymphatics follow the deep blood vessels, namely, the radial, ulnar, and dorsal interosseus chains. The drainage is to the axilla. The lymph drainage of the axilla and the breast usually is to five areas. (1) The anterior (pectoral) group of nodes are in the lower quarter of the pectoralis minor muscle near the lateral thoracic artery and drain the anterior and lateral thoracic walls and the central parts of the breast. (2) The lateral nodes are in relation to the axillary veins and drain all but the cephalic side to the subclavicular and inferior cervical nodes. (3) The posterior (subcapsular) group of nodes are close to the subscapular artery draining the skin and muscles of the back and neck to the central axillary nodes. (4) The central (intermediate) nodes at the base of the axilla drain all the other nodes. (5) There is a fifth group of nodes (subclavicular or medial nodes) posterior to the pectoralis minor and these drain all the other nodes and the outer parts of the breast. Some of the lymph pathways skip these nodes and pass directly into the thoracic ducts. There is, however, a definite anatomical reason for involvement of the lymph nodes of the axilla in all but early breast malignancy.

Etiology

Lymphedema of the upper extremity may be caused by any of the conditions which cause lymph stasis in the lower extremity. 1. Primary lymphedema is caused by specific organisms which invade the lymphatic system. These are the Wuchereria bancrofti, the Mycobacterium tuberculosis, or the Treponema pallidum. 2. A secondary infectious lymphedema may come from any of the usual septic organisms or even from fungus infection. 3. Traumatic lymphedema may result from a laceration or trauma causing a thrombosis of the lymphatic channels. Some of these injuries may be due to prebirth or labor trauma. 4. Malignancy may cause lymphedema at any area. The commonest cause of such lymphedema in the upper extremity is carcinoma of the breast or operations and radiation therapy for it subsequently. 5. Allergy may cause lymph stasis due to some specific antithesis. 6. Subsequent venous thrombosis may also be a cause for lymphedema, since this causes an overload on the lymph drainage. An example is the so-called "milk leg." 7. Congenital lymphatic collections are well recognized. They may occur as a cystic hydroma or the essential or Milroy's type in the arm or leg.

Pathology

A nonmalignant lymphedema of the upper extremity may follow radical breast operations, owing to operative trauma and the removal of the lymph channels and nodes. In addition there may be edema from some temporary interference with the venous return. Low-grade infection also may be a cause of temporary postoperative swelling.

Sometimes also the lymphatic channels are closed completely, either by surgery or ray therapy, and then the lymph collections will be continuous. It is with lymphedema of this traumatic type as well as of the congenital type that this discussion will deal.

Symptoms

The symptoms are mainly a massive enlargement of the part. To this swelling are added the skin changes, muscle atrophy, and sometimes damage to nerves from pressure and a pull on the shoulder girdle, which come with inadequate drainage of the part. The lymph accumulates in the skin, fat, superficial fascia, and deep fascia, but rarely is there any collection in the muscle except in the fat which may be in and around the muscles. The vascular infiltration of the lymph spaces is soon replaced by fibrous tuberculae forming a framework which maintains an area in which the lymph collects. Collagen may be fragmented as may all other structures from the pressure of fluid collection. Ulcerations occur. Usually there are an increased number of

veins as this system tries to carry out the function of the lymphatic system.

Surgical Treatment

The edema due to interference with the venous return can be treated on a mechanical basis by elevation and good support.

For the lymphedema due to infection the use of antibiotics is helpful. Where malignancy involves the nodes and has not been completely removed, the lymphedema will be progressive.

If the lymphedema follows the treatment of a malignancy, this disease must be ruled out by biopsies. If the conservative treatment of elevation, good support, antibiotics (and sometimes interruption of the sympathetics) has failed, surgical excision becomes the treatment of choice.

We found (and reported previously) that the pathologic lymph collections in lymphedema begin approximately at 1/50 to 1/60 in. underneath the epidermal layer. The epidermis superficial to such lymph collections is not diseased and can be removed by the electric dermatome at 0.0015 in. All of the rest of the superficial and deep fascia is excised to remove all fatty tissue, even that between the muscles. The epidermis is replaced directly on the denuded muscles. The principle of this operation is to remove the skin in such thin layers as not to have lymph accumulations in this skin. Some of the congenital accumulations as well as those after surgery (but not due to malignancy) are shown.

In an effort to demonstrate how extensive nonmalignant arm lymphedema can become with its disabling pathology, the following case and its therapy is reported.

Report of a Case

Twelve years ago a 39-year-old woman had a left radical mastectomy performed for carcinoma. Four days later she complained of swelling in the left hand and arm. On the eighth postoperative day she was discharged with a profuse drainage of lymph from the axilla. Three weeks later she complained of severe pain in the left arm, and she states an "abscess" was drained from the left axilla. She was then given 30 deep x-ray treatments. The swelling of the entire arm became progressively worse. With elevation there was but a slight decrease of swelling of the hand and none of the arm. It was necessary for her to have her arm carried around by her husband and a neighborhood boy.

This patient was admitted to St. Clare's hospital and treated with surgical excision of all the skin at 0.0015 in. The lymph, fat, superficial and deep fascia then were excised with grafting of the removed skin. The operation was done in two stages.

Exactly how much lymph tissue was removed is unknown, but the patient lost 90 lb. in weight. So much fluid ran out during the operation that the surgeon and his assistants were literally "soaked" in lymph and many sheets had to be placed on the floor to absorb the literal bath tubs of lymph.

Results.—This patient's therapy has been effective and her physical and psychic trauma so corrected that it was considered worth while to present this case in this brief discussion of this condition. Other patients so affected exist and undoubtedly are in need of relief.

The operation has been performed on 14 other patients, with lymphedema and hemangiomas or arteriovenous fistulas seen increasingly often. Because of the extensive nature of the operation and the resultant scarring, it is suggested that it be reserved only for those patients who are not amenable to any other type of therapy.

Postoperative Care

The patient must have good support to the part, especially the hands, probably indefinitely. There is often some hyperkeratinization, since the epithelial layer is so thin it frequently heaps up with some keloiding. Dermatitis develops, and the patients are subject to fungus infections which we control with soaks of mild solutions of potassium permanganate. Due care must be taken to avoid contracture of the fingers, elbow, and shoulder during recovery. Since the lymph defense is removed, in those patients with repeated attacks of sepsis, antibiotics at regular intervals often are required.

Summary

Lymphedema of the upper extremity is described.

Some data on its pathogenesis are offered.

The importance of knowing the cause of lymphedema as well as the anatomy must be understood.

Congenital collections and operative or ray trauma are the two commonest groups requiring surgical treatment.

The therapy of a patient with an unusually extensive lymphedema is reported.

Surgical therapy successful in 14 patients is presented.

20 East 68th Street (21).

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ADDITIONAL DISCUSSION

ON PAPERS BY DRS. PRATT AND LEVINE AND MURPHY, HAGLIN, EMERSON, AND FELDER*

DR. PAUL T. DECAMP, New Orleans: I should like to discuss the second paper and commend Dr. Murphy on the very excellent study he made. It is one of the very few studies with long term follow-up of this type of procedure. I don't think many of us are using this type of procedure now, but I believe when we consider it, we should ask ourselves just what physiological alteration we are trying to achieve by this operation. This was not mentioned in the discussion this afternoon but I hope it is in the manuscript. The one value to the operation suggested by those who have endorsed it, has been that the ambulatory venous hypertension will be reduced by the operation. It seems strange that the groups interested in this procedure and who have obtained rather detailed visualization studies, which are time consuming and sometimes difficult, have not done more physiological studies in respect to the actual measurement of ambulatory venous pressures in these patients after operation.

Consideration of the facts will allow one to realize that if the venous hypertension in the extremity results from incompetence of valves in the venous system, the only way that this hypertension can be improved permanently would be to introduce valves into the system without obstructing blood flow. There is no other way it can be done. Ligation of the channel will not do it. I might make this more graphic by pointing out that no one has suggested that we completely ligate the orifice of the mitral valve nor that of the aortic valve, for insufficiency. A ligature is not a valve. I do not believe anyone has demonstrated ever that it has reduced the ambulatory venous pressure.

* This article and a portion of the discussion on the two papers were published in the January issue of the ARCHIVES.

Partial Hepatectomy Employing Differential Hypothermia

An Experimental Study

LT. CHARLES E. HUGGINS (MC) and LT. EDWIN L. CARTER (MC), U.S.N.R.

Introduction

Surgeons attempting hepatic resection are confronted with the problem of hemostasis in an extremely vascular and friable organ. Oozing from the cut surface of the liver results in considerable blood loss and obscures the operative field, making control of hemorrhage difficult.

There are numerous indications for an improved technique for partial hepatic resection. One such indication is primary carcinoma of the liver. Halpert and Erickson report an apparent or real increase in the incidence of this neoplasm.[1] In their series of 28 cases from an autopsy population of 1400, the tumor is believed to have been the direct cause of death in 16. Thirteen patients died without evidence of distant spread of the disease.

Embolic metastatic lesions frequently involve the liver and, while usually multiple, may be solitary. Neoplasms of the gallbladder, stomach, and colon are occasionally found to extend directly into the liver, and good results have been reported following removal of the primary lesion in continuity with attached portions of the liver.[2] Vascular anomalies,[3] cysts, and benign tumors are additional indications for partial resection of the liver.

The present report is concerned with the physiologic and pathologic studies undertaken in an attempt to devise an improved technique for partial hepatic resection.

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The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the view of the Navy Department or the Naval Service at large.

Methods and Results

Part I

Seventy-seven male mongrel dogs, unselected as to age and size, were used in the initial part of this study. Weights ranged from 10.0 to 28.6 kg., with a median weight of 17.7 kg. All operations, except where specifically indicated, were performed with aseptic technique under intravenous pentobarbital sodium anesthesia. A midline abdominal incision was used in all cases. This incision was extended by splitting the sternum in the midline if additional exposure was required. Intermittent positive pressure artificial respiration with 100% oxygen was maintained while the pleural spaces were open. For the first three to four hours following chest closure, intermittent aspiration of the pleural spaces was performed via an indwelling 22 F. Foley catheter.

Both preoperative and postoperative diets consisted of standard kennel pellets and water ad libitum, with the addition of 1 lb. (0.45 kg.) of ground horsemeat daily. Neither antibiotics nor intravenous fluids were given preoperatively, and, except where specifically stated, neither was given postoperatively.

All animals were observed for a period of three weeks postoperatively. Sulfobromophthalein (Bromsulphalein) retention tests (5 mg. dye/kg., blood sample analyzed 45 minutes after injection) were performed near the end of the first week and again prior to killing. At autopsy, specimens of liver, kidney, and intestine were fixed in magnesium carbonate-saturated 10% formalin for histological preparation.

The experiments in this part of the study were divided into eight groups.

Group I. Selective Cooling of the Liver

Stimulated by reports of successful hepatic resection employing general hypothermia and hepatic afferent vascular occlusion,[4] we undertook these studies to determine whether similar results

could be obtained employing selective cooling of the liver. Plastic cannulae were inserted into the splenic artery and splenic vein in each of eight dogs. A siliconed glass coil was interposed between the cannulae, and then the arteriovenous shunt was opened. The blood flowing through the shunt was refrigerated by circulating iced brine through an outer jacket around the coil. The liver temperature fell rapidly. Although establishment of the shunt was proved technically feasible and cooling took place rapidly, clotting always occurred within the coil (Table 1).

TABLE 1.—*Summary of Results in Groups I and II*

Group	Procedure	Mortality (No./Total)
I	Blood cooling of liver alone	8/8
II	Portal vein occlusion, 60 min.	8/10

It appeared that this technique would not be practical without modification. Two questions presented themselves: First, could the gastrointestinal tract tolerate the congestion that would follow occlusion of the portal vein in the porta hepatis for one hour? Second, if the gastrointestinal tract tolerated the necessary portal vein occlusion, could a modification of the technique be devised that would permit the blood cooling without clotting?

Group II. Portal Vein Occlusion

To answer the first question, 10 animals were subjected to occlusion of the portal vein for one hour at a point between the entrance of the coronary vein and the bifurcation of the portal vein in the porta hepatis. Eight of these animals died within 48 hours following the procedure. The other two animals recovered rapidly and appeared healthy at the time of killing. All animals passed gross blood by rectum, and most animals vomited blood as well. Postmortem examination of the animals that died revealed a dark blue discoloration of the stomach and intestines, engorgement of the spleen, and a soft pale liver. Microscopically, the intestines showed hemorrhage throughout the mucosa. The two surviving animals had sulfobromophthalein retention of less than 5% after 45 minutes and normal appearing viscera grossly and microscopically at the time of killing.

It was apparent that any technique for hepatic surgery based on selective cooling of the liver with subsequent interruption of its afferent circulation must provide for the damaging congestive effects of portal occlusion on the gastrointestinal tract.

Group III. Intraperitoneal Cooling

It seemed reasonable that cooling of all the peritoneal contents might prevent the intestinal damage following temporary total hepatic afferent vascular occlusion. The large area of the mesentery would act as a heat-exchanging surface, cooling the blood flowing to the liver.

Accordingly, 10 animals were subjected to intraperitoneal cooling. Sterile saline at a temperature of 2-10 C was poured into the peritoneal cavity until the abdomen was filled. The viscera were gently agitated to provide uniform distribution of the saline, which was then aspirated. This cycle was repeated until 8-10 liters of saline had been used. Fluid that was aspirated from the peritoneal cavity was discarded. Liver and intestinal temperatures fell below 25 C within 10-15 minutes.

One hour following the last insertion of cold saline, 4 liters of warm saline at a temperature of 40-45 C was poured into the peritoneal cavity and aspirated. The abdomen was closed in the usual manner.

All 10 animals recovered promptly and were healthy and without evidence of infection at the time of killing (Table 2). Sulfobromophthalein-retention tests performed three to five days postoperatively and again at the time of killing showed less than 5% retention. Gross and microscopic examination of the abdominal viscera were unremarkable.

This type of cooling appeared safe and did not predispose animals to infection. However, for such a technique of cooling to be of practical value in hepatic surgery, it would be necessary to occlude the circulation proximal to the cooled viscera in order to decelerate temperature equilibration with the rest of the body.

TABLE 2.—*Summary of Results in Groups III to VII*

Group	Procedure*			Mortality		Survival
	A	B	C	48 Hr.	2 Days-3 wk.	No./Total
III	X			0	0	10/10
IV a		30		0	0	5/5
b		60		9	0	1/10
V		60	X	6	0	4/10
VI	X	60		0	7	3/10
VII	X	60	X	0	0	10/10

* A, intraperitoneal cooling; B, aortic occlusion above celiac axis and portal vein occlusion, duration in minutes; C, support—Postoperative I.V. fluids and antibiotics.

Group IV. Aortic Occlusion at Normal Temperature

Arterial circulation to the gastrointestinal tract and liver may be interrupted by occluding the aorta proximal to the celiac axis or by simultaneously occluding the celiac axis and the superior and inferior mesenteric arteries. Since the former site appeared to offer a more rigorous test for any technique designed to prevent ischemic damage, it was selected for use in subsequent experiments.

In each of five dogs the aorta, just cephalad to the celiac axis, and the portal vein, as it enters the porta hepatis, were simultaneously occluded for a 30-minute period. Three of the 5 animals passed small amounts of blood and mucoid material by rectum postoperatively, but none died. All animals appeared healthy and had sulfobromophthalein retention of less than 5% at the time of killing. Their abdominal viscera appeared normal to gross and microscopic examination.

Ten animals were next subjected to similar occlusion of the aorta and portal vein for 60 minutes. All passed large quantities of bloody mucoid material by rectum, and 9 of the 10 animals died within 48 hours. None was paraplegic. Autopsy of the animals that died revealed large quantities of blood in the intestinal tract. An acute necrotizing enteritis with necrosis of the tips of the intestinal villi and mucosal hemorrhage was seen histologically. The central portion of the liver was soft, and the tips of the lobes were dark. Histologically, the liver revealed marked central congestion and hemorrhage with dissociation of the hepatic cords and cellular vacuolation. Grossly the kidneys were dark red, with a particularly dark band at the corticomedullary junction. Histologically, they showed minimal degeneration and necrosis of the proximal tubules and moderate necrosis of the loops, ascending limbs, and distal tubules. The entire organ was hyperemic.

The one animal that survived was very ill initially but recovered and appeared normal before killing. Sulfobromophthalein retention was less than 5%, and the abdominal viscera appeared normal to gross examination when the animal was killed at three weeks. Histologically, there was an exudate of lymphocytes and segmented neutrophils in the portal areas. The kidneys showed minimal pyelonephritis. These changes may or may not have been related to the experimental conditions.

Group V. Aortic Occlusion at Normal Temperature with Postoperative Supportive Therapy

In view of the results in Group IV, it seemed worth while to evaluate the efficacy of supportive measures in preventing death from temporary interruption of blood supply to the abdominal viscera. Ten animals were subjected to 60-minute occlusion of the aorta and portal vein, as in Group IV. After removal of the clamps and wound closure, they were given the following: 1000 cc. 0.85% saline intravenously, 0.2 gm. of chlortetracycline (Aureomycin) HCl intravenously, and 1,500,000 units of procaine penicillin G with 1.0 gm. of dihydrostreptomycin intramuscularly. Surviving animals were

given 500 mg. of chlortetracycline orally, once daily, for five days.

Four of the ten animals survived and appeared healthy before killing. Sulfobromophthalein retention was less than 5% prior to killing. Histologic changes were similar to those seen in the one animal in Group IV that survived the procedure without supportive therapy. Leucofuchsin stain demonstrated little glycogen to be present in the liver.[5]

The pathological picture in the six animals that died was similar to that seen in the animals that did not receive supportive therapy.

There did not appear to be any essential difference in the pathology between Groups IV and V. Blood transfusions and more vigorous intravenous fluid management might have further lessened the mortality following aortic occlusion.

Group VI. Intraperitoneal Cooling Followed by Occlusion of the Aorta and Portal Vein

Ten animals were subjected to intraperitoneal cooling as in Group III in an attempt to obtain a level of hypothermia sufficient to protect the animal from the deleterious effects of one hour of occlusion of the abdominal aorta and portal vein. The inferior vena cava just below the entrance of the renal vein was occluded during the period of active cooling in order to decrease the amount of blood passing through the abdomen. Near the end of the 10-15 minute active cooling period, the aorta and portal vein were occluded as in Group IV. One additional liter of cold saline was then poured into the abdomen to assure maximal cooling. The viscera were gently agitated, and all saline was aspirated. The occluding clamps were removed 60 minutes after their application. Intraperitoneal warming was then carried out with saline at 40-45 C, and the abdomen was then closed. If the esophageal temperature was below 32 C, rewarming was speeded by partial immersion of the dog in a bath of water at a temperature of 40-45 C. Otherwise the dog was permitted to warm spontaneously with the aid of two electric heating pads and a woolen blanket.

All animals were active on the morning following surgery. None demonstrated gastrointestinal hemorrhage, diarrhea, or paraplegia. Seven of the ten animals appeared ill 48 hours following surgery and became progressively more so until their death, 3 to 15 days postoperatively. These dogs died from infectious complications, four with peritonitis and three with pneumonia.

The three survivors were healthy and active at the time of killing. The liver, kidneys, and intestines in these surviving animals appeared normal grossly and microscopically.

It appeared that intraperitoneal cooling protected the animals from the gastrointestinal hemorrhage associated with interruption of aortic circulation for one hour but not against a breakdown of the normal resistance to infection caused by ischemia.

Group VII. Intraperitoneal Cooling Prior to Occlusion of the Aorta and Portal Vein with Postoperative Supportive Therapy

Ten dogs were subjected to the same procedure used in Group VI, followed by the same postoperative supportive regimen given the animals in Group V. All 10 dogs in this group were awake and active the morning following surgery and remained healthy until the time of killing. Sulfobromophthalein tests were normal when performed three to five days postoperatively and again three weeks following the operation. Histologically, the liver, kidneys, and intestines appeared normal to both gross and microscopic examination.

Group VIII. Hemodynamic Studies

Hemodynamic studies were carried out on a group of four dogs as nonsterile acute experiments. The carotid artery, external jugular vein, femoral artery, and femoral vein were cannulated as preliminary procedures. Arterial blood pressures were measured with a Statham strain gauge which was calibrated with a mercury manometer and recorded on a Sanborn twin-Viso recorder. Venous pressures were measured with saline manometers. A copper-constantan thermocouple was placed in the midesophagus for measurement of general body temperature. After base line readings had been obtained, the abdomen was opened and the portal vein was cannulated via the splenic vein for measurement of portal pressure. Thermocouples enclosed within No. 13 G needles were placed in a dependent loop of intestine and the central portion of the liver. Temperatures were recorded simultaneously on a Brown recording potentiometer.

Intraperitoneal cooling with simultaneous occlusion of the inferior vena cava below the renal vein was followed by occlusion of the aorta above the celiac axis and occlusion of the portal vein as it enters the liver. Circulatory interruption was maintained for one hour, at the end of which time the clamps were quickly released. Intraperitoneal rewarming was carried out with saline at 40-45 C.

Initial temperature readings of all thermocouples were between 36 and 37 C. Temperatures of the liver and bowel fell precipitously when the abdomen was filled with cold saline. The fall in the intestinal temperature always preceded that of the liver. As the peritoneal cavity was evacuated, both temperatures rose 2-4 C, only to fall again as more saline was introduced. Within 6 to 9 minutes both bowel and liver temperatures were below 25 C (Fig. 1). After 10-12 minutes of cooling, the intestinal temperature was 17-20 C and the liver temperature was 20-24 C. Esophageal temperature fell gradually after active cooling had begun and was 30-32 C by the time the occluding clamps were released. When warm saline was poured into the peritoneal cavity, there was a rapid rise in bowel and liver temperatures, with the change in the bowel again preceding that in the liver. Following intraperitoneal warming, all temperatures rapidly equilibrated between 31-34 C. A mercury thermometer (−10-200 C) was used in addition to the thermocouples and was found to be quite serviceable for measurement of bowel and liver temperatures. This instrument may be autoclaved.

Carotid and femoral arterial blood pressures were equal except during the period of aortic occlusion. Initial mean pressure readings were in the range of 120-150 mm. of mercury. With intraperitoneal cooling, blood pressure fell to 90-110 mm. Hg, with a curve similar to the fall in esophageal temperature. When the aorta was clamped, the carotid pressure rose quickly to a level slightly higher than it was before cooling, namely, to 130-160 mm. Hg (Fig. 2). Femoral arterial pressure fell to 10-30 mm. Hg. During the 60-minute period of aortic occlusion, there was a gradual fall in carotid pressure and rise in femoral pressure, each of about 10 mm. Hg. After release of the aortic clamp there was a precipitous fall in mean carotid pressure to 40-60 mm. Hg. However, within 90 seconds arterial pressure returned to a level slightly less than before occlusion. These

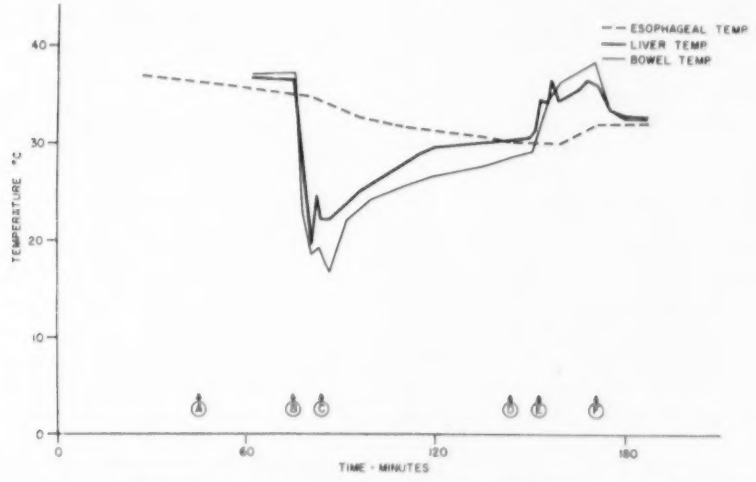

Fig. 1.—Representative temperature changes in the liver, intestine, and esophagus of one dog during intraperitoneal cooling and aortic occlusion. Point *A*, control values; Point *B*, intraperitoneal cooling begun, inferior vena cava occluded; Point *C*, aortic occlusion above the celiac axis, inferior vena cava released; Point *D*, aortic clamp, released; Point *E*, intraperitoneal warming begun; Point *F*, spontaneous rewarming.

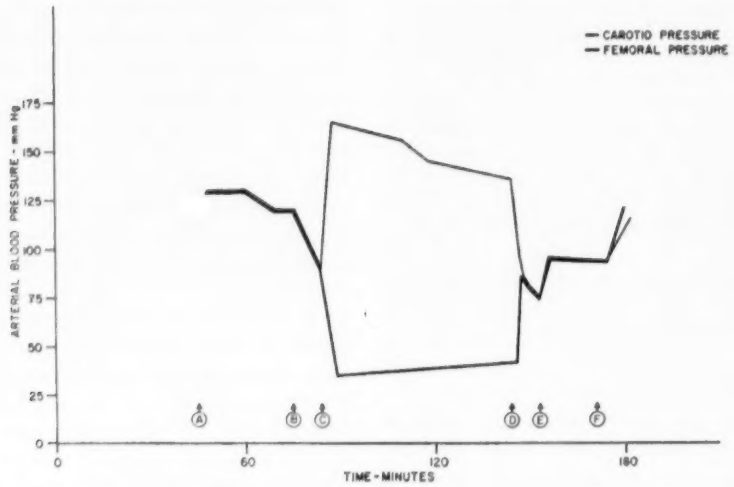

Fig. 2.—Representative arterial pressure changes in the carotid and femoral arteries of one dog during intraperitoneal cooling and aortic occlusion.

pressures rose further wtih introduction of warm saline and continued to return toward normal levels as the animal warmed.

There was no significant change in jugular venous pressure during the experiment (Fig. 3). A transient rise in femoral venous pressure occurred during inferior vena caval occlusion, but this pressure was otherwise normal throughout the procedure. Pressure in the portal vein rose gradually during the period of aortic and portal venous occlusion. In one instance this reached 35 cm. of isotonic saline but generally did not rise above 25 cm. This pressure was always within normal limits before and after occlusion.

Liver, intestinal, and esophageal temperature studies, as well as sterile carotid arterial and portal venous pressure measurements, were later carried out on 15 dogs

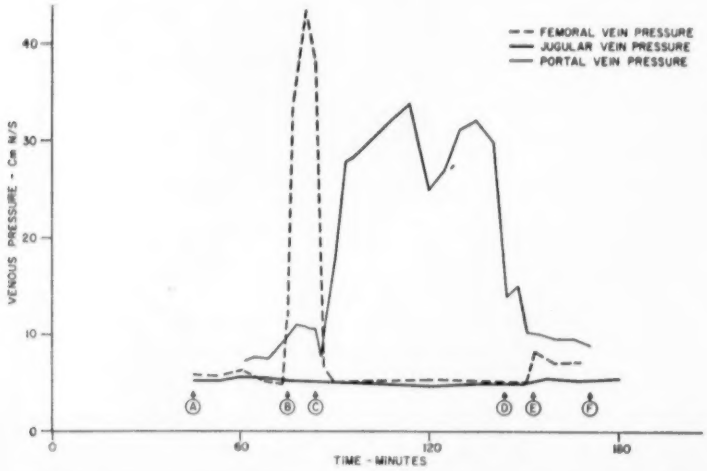

Fig. 3.—Representative venous pressure changes in the jugular, femoral, and portal veins of one dog during intraperitoneal cooling and aortic occlusion.

with partial hepatic resection. The changes in temperature and blood pressure in these dogs were within the limits described in the present group.

Part II. Hepatic Resection Employing Differential Hypothermia

Thirty animals were used in this part of the study. They underwent intraperitoneal cooling with subsequent occlusion of the aorta above the celiac axis and portal vein between the coronary vein and the porta hepatis. Resections of 15% to 90% of the liver were carried out during the period of circulatory interruption.

The avascular ligaments of the liver were divided to facilitate exposure. Resection was performed without attempting to clamp intrahepatic vessels before transection. These operations were characterized by absence of oozing from the liver substance. This made identification and clamping of the large vessels easy. Macroscopic vessels and bile ducts were stitched or ligated with 000 braided nonabsorbable surgical (silk) sutures. Resection and definitive hemostasis required 11-25 minutes for completion. In 26 animals, occlusion of the aorta and portal vein was maintained for one hour regardless of the time required for surgery. With release of the occluding clamps, occasional minor bleeding points appeared and were sutured and ligated. In the other four animals the clamps were released as soon as hemostasis had been obtained following resection. No oozing occurred in these cases.

After release of the clamps and suture of open vessels, warm saline was poured into the peritoneal cavity, following which the liver was again inspected for bleeding. No artificial covering for the raw surface was used, nor was any attempt made to approximate the cut edges. The abdomen was closed without drainage. The same postoperative supportive regimen was administered as in Groups V and VII of Part I.

Eight of the thirty animals that underwent partial hepatic resection died. Four animals died within 48 hours postoperatively from the following causes: pneumonia, pneumothorax, pancreatitis, and hepatic insufficiency secondary to 90% resection. Vigorous retraction near the porta hepatis was necessary to expose this region during the filming of a movie and probably caused the pancreatitis.

The other four animals died between 11 and 18 days postoperatively from the following causes: enteritis with perforation, jejunojejunal intussusception, distemper, and peritonitis. The animal that died from distemper did well for the first few days and had a sulfobromophthalein retention of less than 5% one week after operation. At autopsy his abdominal viscera appeared normal. No definite cause could be found for the peritonitis in the fourth animal. There was no evidence of biliary leakage.

The remaining 22 animals were strong and healthy at the time of killing. Hypertrophy of the liver remnant was most marked in animals that had the largest resections. There was no impairment of sulfobromophthalein retention in animals that underwent less than 50% resection. Removal of greater than 50% of the liver frequently resulted in sulfobromophthalein retention of as high as 50% when the test was performed one week postoperatively. With few exceptions sulfobromophthalein retention had returned to normal by the time of killing. These animals were frequently lethargic the day after surgery, and exhibited anorexia, hyperpnea, and mild ascites. This picture cleared rapidly and the animals appeared normal within three to five days.

Neither paraplegia nor gastrointestinal hemorrhage was seen in any of the dogs. With the possible exception of the one animal that died of peritonitis, there was no case of postoperative bleeding, biliary leakage, or complications attributable to the large raw liver surface.

Comment

The criteria for a successful technique of partial hepatectomy should include the following: First, the surgeon should have a minimum of 60 minutes for the performance of deliberate hepatic surgery. Second, ancillary procedures employed to grant the surgeon this time must be simple, add negligible risk, and result in no permanent damage. Third, there should be no impairment of normal liver regeneration. Fourth, bleeding and biliary leakage should be controlled by individual ligation of vessels and bile ducts rather than by a technique of

mass hemostasis. Fifth, neither devitalized liver tissue nor foreign bodies should remain at the site of resection.

In addition to the above, it is desirable that the technique permit immediate, one-stage removal of hepatic lesions discovered at the time of laparotomy. For widespread use, such procedures must be applicable in small community hospitals as well as large medical centers.

The great vascularity of the liver makes hemostasis following hepatotomy a difficult problem. This problem may be approached in one of three ways. First, one may attempt to obtain hemostasis without resorting to extrahepatic procedures. Many currently employed methods of hepatic surgery utilize this approach and depend for their success on mass hemostasis prior to or at the time of resection. Sklifosovsky attempted to control bleeding by first partially exteriorizing the liver.[6] The protruding tissue was then removed by gradual tightening of a strangulating tourniquet. More recently, surgeons have tried to obtain hemostasis by the use of through-and-through mattress sutures. Compression plates used with such sutures decrease their tendency to cut through the delicate capsule.[7] Temporary application of gauze packs [8] or absorbable sponge material has helped to control residual oozing.

Coagulation of hepatic tissue subjacent to a line of resection has been employed to secure mass hemostasis. Cautery excision of small peripheral lesions has been used with some success.[9,10] Serra and Brunschwig have recently reported an interesting variation of the coagulation technique in which a large hollow knife filled with liquid nitrogen (boiling point −193 C) was employed to freeze a zone of liver tissue 0.5-3.0 cm. from the resection edge.[11] Such techniques of mass hemostasis do not permit careful and accurate dissection, and may predispose to infection as well as secondary hemorrhage.

The second approach that one may employ to facilitate hepatic surgery is to obtain a dry field by diversion of blood flow. Total circulatory by-pass of the liver would be difficult to accomplish technically and could be maintained for brief periods only. As a result, most attempts have been directed toward diversion of only the portal flow. This can be accomplished directly by means of an Eck fistula (portocaval anastomosis with ligation of the portal vein and its branches between the fistula and the liver). Indirect diversion of the portal blood into the systemic circuit via collateral channels may be accomplished by gradual portal vein occlusion. Oré described an experimental technique for such occlusion in which he passed a loop of thread about the portal vein and brought the long ends out through the incision. Division of the vein was accomplished by exerting daily traction on these ends. By the 10th or 12th day the loop could be withdrawn intact, indicating section of the portal vein.[12] Brunschwig has applied this technique to man.[13] The procedure has the disadvantage of requiring two to three weeks between stages and results in complete thrombosis of the portal vein. During the period of gradual occlusion there may be a compensatory increase in hepatic arterial flow with little resultant change in total afferent flow.[14,15]

Both of the above techniques for portal diversion require major surgery prior to hepatic resection and by themselves accomplish only partial devascularization of the liver. Mann et al. have suggested that permanent diversion of the portal blood supply leads to atrophic changes in a previously normal liver, as well as impairment of normal regeneration following partial hepatectomy.[16]

The third approach that may be employed to facilitate surgery of the liver is temporary interruption of its blood flow. Such interruption may be applied to the entire organ or to individual lobes. DeWeese reported that, in dogs, permanent ligation of the branch of the portal vein supplying two of the three major lobes, and temporary occlusion of the common hepatic artery, permitted relatively bloodless removal of portions of the devascularized lobes.[17] However, microscopic sections revealed atrophy and degen-

erative fatty changes in the cells of the remaining segment deprived of portal blood. Lortat-Jacob and Robert [18] and Hubard and Meyer-May [19] have demonstrated clinically that preliminary ligation of the appropriate lobar branches of the portal and hepatic veins and the hepatic artery reduces hemorrhage when an entire lobe is resected. The numerous anatomical anomalies of the hepatic artery and portal vein might make these procedures difficult, especially in patients with hepatomegaly or pathology in the porta hepatis.[20-22]

Blood flow to the liver may be interrupted either proximal to the gastrointestinal tract or in the porta hepatis. Occlusion at either site for one hour, at normal temperature, results in a very high mortality.[23-25] The pathological picture is that of hepatic ischemia and either ischemia or congestion of the gastrointestinal tract and spleen, depending on the point of occlusion.

Raffucci and Wangensteen reported that 20 minutes was the maximum period of occlusion of the hepatic artery and portal vein tolerated by dogs without evidence of hepatic necrosis.[26] Our studies indicate that relatively short periods of portal vein occlusion alone, at normal temperature, result in a high mortality. Drapanas et al. demonstrated that, if the deleterious effects of portal congestion on the gastrointestinal tract are prevented by preliminary establishment of an Eck fistula, dogs will tolerate 75 minutes of total hepatic afferent vascular occlusion in the porta hepatis.[27] Any technique for hepatic surgery employing vascular interruption in the porta hepatis must provide protection against portal bed congestion.

Arterial occlusion proximal to the gastrointestinal tract avoids the complication of portal bed congestion but substitutes the problem of ischemia. Burch et al. and Edwards et al. have demonstrated that one hour of occlusion of the aorta above the celiac axis results in a very high mortality.[23,24] Our studies confirm their observations. Burch has further demonstrated that if the metabolic requirements of the liver are reduced by local cooling of the liver, achieved by wrapping the organ with refrigerated coils, dogs will tolerate one hour of occlusion of the aorta at the level of the diaphragm. As mentioned above, Drapanas demonstrated that dogs will tolerate one hour of hepatic ischemia if vascular congestion of the gastrointestinal tract is eliminated. It would thus appear that dogs will tolerate one hour of ischemia of either the gastrointestinal tract or the liver, at normal temperature, but not both simultaneously.

Major advances in the field of hepatic vascular interruption have awaited the advent of controlled hypothermia. Pontius demonstrated that the descending thoracic aorta could be occluded for one hour with survival in the majority of cases.[28] Bernhard et al. and Shumway and Lewis have reported successful partial hepatic resection utilizing general hypothermia and proximal vascular occlusion.[4,29]

Pierpont and Blades demonstrated that flooding the pleural space with cold sterile saline produced general body cooling.[30] This was accomplished at the time of thoracotomy after the local pathology and been evaluated. These authors have reported no long-term complications from their technique.[31] Kjelgrenn and Churchill-Davidson et al. have reported the experimental use of intraperitoneal cooling by means of refrigerated coils or cold saline to obtain general hypothermia.[32,33]

In the presently reported technique for differential cooling of the abdominal viscera, there appears to be direct conduction cooling of the gastrointestinal tract and, to a lesser degree, of the liver and spleen. Circulation of the refrigerated portal blood through the liver results in a rapid fall in its temperature. The extreme rapidity with which changes in the temperature of the liver follow those of the intestinal tract demonstrates the effectiveness of the mesentery as a heat-exchanging surface. Circulatory isolation of the abdominal viscera afforded by afferent vascular occlusion decreases the rate

of temperature equilibration. The effectiveness of intraperitoneal cooling and proximal vascular occlusion depends on extremely rapid cooling and slow equilibration. This results in minimal general hypothermia. Hepatic resection may be performed during the period of afferent vascular occlusion with great ease and low mortality. Antibiotic therapy postoperatively reduces the incidence of sepsis.

Shumway and Lewis have stressed the desirability of interrupting hepatic efferent circulation during the performance of hepatic resection in order to decrease blood loss and prevent air embolism. Complete interruption of hepatic efferent circulation is difficult to accomplish unless the inferior vena cava is occluded above and below the liver. Shock and death due to pooling of blood in the lower extremities rapidly follow this procedure unless the aorta is simultaneously clamped at a high level (T 8-T 10). Hypothermia does not protect against the development of shock under such circumstances.[34] This level of aortic occlusion might be associated with an increased incidence of spinal cord complications.[35] Furthermore, the long distance between the site of aortic occlusion and the liver allows anastomosis between many collateral vessels and decreases the effectiveness of hepatic arterial interruption. This is a possible explanation for the arterial bleeding noted by Shumway and Lewis but not seen in our dogs.[29]

No attempt was made to interrupt hepatic efferent flow in our animals during partial hepatectomy. Although small amounts of air entered the venous system, none of the animals demonstrated any deleterious effects. In our experience, blood generally flowed out of the vein rather than air into it. If the surgeon bears in mind the possibility of air embolism and clamps the hepatic veins as they are encountered, very little air enters the systemic venous system. The amount of bleeding from the hepatic veins was not great nor did it make hemostasis difficult.

Since much of the hepatic cooling results from the inflow of cooled portal blood rather than by direct conduction cooling, and since the vascular anatomy of the gastrointestinal tract of the human is similar to that of the dog, one would expect this technique to be applicable in man. Cooling progressed satisfactorily in one of our dogs that weighed 105 lb. (47 kg.). If applicable in humans, this technique would offer certain advantages over the use of general hypothermia for partial hepatectomy. First, it would allow immediate, one-stage resection of hepatic lesions discovered at laparotomy. Second, it would permit the surgeon to evaluate resectability of hepatic lesions without committing the patient to general hypothermia or a staged operation. Third, the minimal degree of general hypothermia would decrease the incidence of cardiac complications and postoperative hemorrhage. Fourth, the simplicity of the technique would permit its use in community hospitals as well as large medical centers.

Summary and Conclusions

One-hour occlusion of both the abdominal aorta above the celiac axis and the portal vein as it enters the liver proved fatal for 9 of 10 normothermic animals. If intravenous fluids and antibiotics were given postoperatively, the mortality was decreased to 6 of 10 dogs. Although supportive measures following aortic occlusion appeared to improve the survival rate, the fundamental pathology remained unaltered.

The gastrointestinal hemorrhage, liver damage, and death in normothermic control animals following 60 minutes of aortic occlusion above the celiac axis is prevented by preliminary intraperitoneal cooling and postoperative supportive measures.

Intraperitoneal cooling, as performed in these experiments, was safe and did not predispose animals to infection. Fall in the temperature of the gastrointestinal tract and liver was rapid, and the rate of equilibration with the rest of the body was slow.

An experimental technique for partial hepatectomy employing intraperitoneal cooling and hepatic afferent vascular occlusion

is presented. The technique is simple and potentially offers numerous advantages over general hypothermia.

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Editorials

Reseach, Investigation, and Teaching in the Armed Forces Medical Services

In this issue of the A. M. A. ARCHIVES of SURGERY will be found a paper on "Experimental Hepatic Surgery Employing Differential Hypothermia" by two young medical naval reserve officers on active duty at the U. S. Naval Medical Research Institute in Bethesda, Md. Their exhibit on the same subject won one of the Certificates of Merit in the scientific exhibit section at the recent A. M. A. meeting. In this issue also will be found an editorial on "The Army Residency Training Program in Surgery," which has been so effectively carried out at the Brooke Army Hospital, and one on "Surgical Teaching and Investigation in the United States Air Force."

All of these contributions are examples of the fine work being done in the hospitals and research centers of the armed forces, where facilities for research, clinical investigation, graduate training, and medical therapy are worthy counterparts of similar activities in civilian hospitals and university and clinic teaching centers.

Dr. Frank B. Berry, Assistant Secretary of Defense for Health and Medicine, has a group of distinguished civilian medical consultants who meet with him regularly at different armed forces medical installations twice a year. Dr. Clifford C. Furnas, Assistant Secretary of Defense for Research and Development, has a medical sciences panel of civilian medical consultants among whom are many distinguished American physicians, surgeons, and medical scientists. The chairman of this panel is Dr. Richard Kern, Professor and Chairman of the Department of Internal Medicine of Temple University School of Medicine.

The members of Dr. Furnas and Dr. Kern's panel meet with Dr. Berry and his civilian medical consultants at the different

armed forces hospitals, research institutes, and schools to observe the work being done in medical treatment, research, and medical specialty training and to comment on it. These consultants have been particularly impressed with the fine instruction being given to the medical officers, the opportunities for clinical investigation and research which are being used to great advantage, and the excellent care being given to patients. Since similar, favorable comments have been made by medical members of other advisory groups, many of whom have also visited the armed forces hospitals abroad and participated in their scientific activities, it seems important that the viewpoint of these civilian medical specialists be given wider dissemination than can be obtained by word of mouth.

In forthcoming issues we will occasionally present to our readers editorials and articles commenting on the medical and other scientific activities in the armed forces. It is to the benefit of our country that close liaison be continuously maintained between the medical services of the armed forces and those of the civilian population. We as civilians benefit from the research and experience of the armed forces and integrate into our practice the knowledge that they have gained. The armed forces do the same with the results of our civilian research. This close liaison also makes active duty more attractive and profitable for the reserve officer and creates a professional atmosphere that is much more satisfactory to those doctors who choose the regular service as a career. As a final point, this liaison permits us to know better the problems of the service doctor, and armed with this knowledge we can help the services attain professional, economic, and management goals for their doctors which will go a long way toward providing the corps of regular physicians necessary to give medical service to our military arms.

WALTMAN WALTERS, M.D.

The Army Residency Training Program in Surgery

Many times the question is asked, "Why should the Army have a residency training program in Surgery?" Basically, especially in peace time, an Army surgical service is like any other surgical service, having the same aims of patient care, teaching, and clinical research. These three elements are almost of equal importance so that if one "leg" of this tripod base is weak, the whole structure is unstable. The mission of the Army Medical Service is conservation of the fighting strength, and from the surgical viewpoint this implies that we must be especially interested and expert in surgery of trauma. Criticism often is based upon incomplete knowledge and understanding of the problems involved. Critics in the service often state that courses in field medicine and greater emphasis on trauma in our residency program would be desirable while civilian inspectors frequently feel on casual glance that we simply duplicate the type of training given in a university center. First, it must be realized that we have recognized the American Board of Surgery as the official certifying agency and therefore our training program is geared to meet or surpass these requirements. To this extent we do duplicate civilian type residency training although we are not in competition with civilian hospitals. At least in peace time, we do not see any more cases of trauma than many of the large municipal charity hospitals and consequently our teaching program covers such cases when they are seen but the bulk of our patients do fall into the university type grouping. It is not appropriate to add "courses" in field medicine to the residency program because a four-year surgical residency is a full time endeavor of itself, and the mission of the Army Medical Service School is to conduct

the training in field medicine. Almost all of our doctors are exposed to this training, but we do make a continuing effort to stress the surgery of trauma at every opportunity. We feel that a good military surgeon has a somewhat broader goal than the civilian general surgeon because the military surgeon must be skilled in general work of the university type, must be especially skilled in the surgery of trauma, must be able to exercise these skills under the most adverse physical conditions, and must have a good understanding of administrative matters such as assignment of soldiers within their physical capabilities and problems of retirement and disability disposition as well as other administrative medical matters. Also, he must be familiar with the various facets of field medicine such as sorting of patients, methods and principles of evacuation of casualties, resuscitation and first aid, and organization and function of various field units, and finally he must be a good amateur practicing psychiatrist. While various individuals have varying interests, all military surgeons must encompass the three fields of professional practice, administrative know-how, and field medicine proficiency. That we meet the professional practice requirement is attested to by the fact that all of our surgical residency programs are fully approved by the appropriate certifying groups and our men make a creditable showing at the specialty board examinations. Administrative know-how is developed in all of our officers from interns to chiefs, but surprisingly enough a recent survey has shown that our residents have a very small administrative burden, devoting most of their time to patient care. Field medicine proficiency is developed when battle casualties are seen and treated or when the cooperative civilian populace engages in the frequent sport of shooting, stabbing, and auto wrecking. Such cases take their proportionate share of time on teaching rounds and we give a yearly seminar of five days' duration covering the various aspects of trauma. Our residents and chiefs are called upon to present papers on subjects in the field of trauma before local groups and over the past six years, some aspect of trauma has been the subject of discussion in 25 to 50 per cent of the weekly surgical seminars in one of our residency training hospitals. It is our belief that residency training in surgery in the Army raises the level of patient care, fosters good teaching, stimulates interest in clinical research, inculcates principles of surgery of trauma, and thus advances the mission of the Army Medical Service—conservation of the fighting strength.

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Medical Research in the Navy

This guest editorial on "Medical Research in the Navy," was written by Dr. Howard T. Karsner, who has been Medical Research Advisor to the Surgeons General of the United States Navy since 1949. Dr. Karsner is a distinguished American scientist whose activities in the field of the medical sciences, whose memberships on the National Board of Medical Examiners and the National Research Council, whose status of consultant to the Secretary of War and the Army Air Forces, and whose activities in the Naval Medical Corps particularly fit him to discuss "Medical Research in the Navy."

WALTMAN WALTERS, M.D.

Medical research in our increasingly important Navy is a major component of the over-all activities of the Department of Defense in research in general and medical research in particular. Maintenance of the health of personnel in peace and war has broad implications as to coordination of the man and the weapons systems, fitness for operations in a wide variety of environments, prevention of disease and injury, diagnosis, and therapy. In some ways this parallels civilian medicine and is accordingly valuable to medical practice as a whole, but many requirements of the military are peculiar to the Armed Forces and need special approaches. However, civilian medicine and military medicine are and should be complementary. The Navy is especially concerned because of its medical support of operations on the sea, under the sea, and in the air, as well as the requirements of Marines on land. The center of the medical effort is the Bureau of Medicine and Surgery, where, under the general direction of the Surgeon General, the Research Division is the focus of this particular kind of medical work.

The Medical Department conducts its research (*a*) in specially designated laboratories, (*b*) in the naval hospitals, and (*c*) through the medium of contracts negotiated by the Office of Naval Research with universities and nonprofit agencies. The largest of the laboratories is the Naval Medical Research Institute, a command in the National Naval Medical Center in Bethesda, Md. Other laboratories of direct operational importance are situated in the Submarine Base at New London, Conn.; the Marine Base at Camp Lejeune, N. C.; Naval Medical Research Unit No. 1, at the University of California; Naval Medical Research Unit No. 2, at Taipeh, Formosa; Naval Medical Research Unit No. 3, in Cairo, Egypt, and Naval Medical Research Unit No. 4, at Great Lakes, Ill. These laboratories are under what is called the management control of the Bureau of Medicine and Surgery. In addition, there are laboratories over which the Bureau exercises technical control in collaboration with other Bureaus of the Navy. These include the School of Aviation Medicine at the Naval Air Station, Pensacola, Fla.; the Aviation Medical Acceleration Laboratory at Johnsville, Pa.; the Air Crew Equipment Laboratory at the Naval Base in Philadelphia; the Naval Radiological Defense Laboratory in the Naval Shipyard at San Francisco; the Navy Mine Defense Laboratory at Panama City, Fla., and the Experimental Diving Unit in the Naval Gun Factory, Washington, D. C. Furthermore, extensive research is conducted under the auspices of the Dental Division of the Bureau, particularly in the Naval Dental School at Bethesda and the Naval Training Center at Great Lakes, Ill.; that of Bainbridge, Md., and that of San Diego, Calif.

A general program is established by the Bureau of Medicine and Surgery, and, on this basis, broad general missions are assigned to laboratories, which in turn initiate projects in support of the mission, and these are correlated in the Research Division of the Bureau. In this way the operation of the program is under constant supervision and precautions are taken to avoid unnecessary duplication of effort.

Research in physiology connected with the operational requirements of the Navy is conducted in various places, but it is especially emphasized at the Naval Medical Research Institute. Microbiology is studied in various laboratories, particularly at Naval Medical Research Unit No. 4, Great Lakes, Ill.; in the Naval Biological Laboratory at the Naval Supply Center, Oakland, Calif.; at Cairo, Egypt, and at Taipeh, Formosa. Pharmacology is studied especially in the Naval Medical Research Institute, but when it is considered that this includes such things as irradiation injury, traumatic injury, burns, and endocrine glands, it is evident that the studies must be widespread in the laboratories and in the hospitals. The same may be said of pathology.

Psychology, psychiatry, and related fields are of the greatest importance in the selection of personnel for such special activities as aviation and submarine operations. Motivation and successful operation must be analyzed with great care. Furthermore, there is a necessity for understanding neuropsychiatric casualties which occur in naval personnel with a view to prevention and correction.

Clinical investigation in naval hospitals is undertaken by those members of the hospitals staffs who have special problems in diagnoses and management which require special attention. In addition, it is now planned to established a Clinical Investigation Center in one or more naval hospitals, where not only do those especially assigned to the centers have fine opportunities for research but these opportunities are also extended to various members of the hospitals staffs including surgeons and related specialists.

Dental research covers investigations of dental caries, periodontal disease, influence of enzymes, the relationship of oral conditions to health, and technical advances in the treatment of oral disease as well as studies of prosthetics. The use of anorganic bone in oral grafting gives great promise.

The Office of Naval Research was established on a broad basis to cover research in the Navy such as that in ordinance, munitions, electronics, etc., as well as work in the biosciences. The work in the biosciences is generally of a basic or supporting type. Thus contracts may be executed with universities and nonprofit agencies so that gaps in knowledge necessary to the solution of operational problems in the service may be overcome.

Naturally, the widespread investigative program is correlated with other activities of the Bureau of Medicine and Surgery. This is particularly true in reference to the Preventive Medicine Division but applies also to Professional, Statistical, and other divisions.

Without attempting to detail all the advances made in medical research, a few examples may be mentioned of interest to the surgical profession. One of these has to do with the preservation of blood. By contract between the Protein Foundation and the Navy, a program is now underway at the U. S. Naval Hospital, Chelsea, Mass., to study the long-term preservation of glycerolated blood at low temperatures. A Cohn fractionator will be installed to study the practical aspects of long-time storage of the red cell mass and deglycerolization for transfusion. Currently it is known that the erythrocyte mass can be preserved for much longer periods than is true of the usual acid-citrate-dextrose (ACD) treated blood. Originating at Naval Medical Research Institute, the Navy supports a study of preservation of blood by means of freezing in liquid nitrogen. This has not yet been so thoroughly investigated

as the biomechanical separation, but when methods of sterile operation and satisfactory thawing are worked out, there is promise that blood can be stored more or less indefinitely, with satisfactory survival of erythrocytes after transfusion.

In collaboration between the Naval Hospital and the Naval Medical Research Institute at Bethesda, Md., work with freeze-dried bone has progressed satisfactorily. At the present time this tissue bank is situated in the Naval Hospital and sufficient amounts of bone are prepared to supply all the needs of the Navy. The method can be adapted to work in civilian institutions. This tissue bank also deals with the preservation of arterial segments, of fascia, and of cadaver skin which can be used after proper preparation for homografting. The work is progressing extremely well and gives promise of many new developments.

Navy surgeons have worked extensively with cardiopulmonary function, and on the basis of the work in two special laboratories, namely, those of the Naval Hospital, St. Albans, N. Y., and the Naval Hospital, Portsmouth, Va., have progressed not merely in the technique of pulmonary resections and in cardiac surgery but have also been able to study the ultimate results of their procedures.

The Navy operates a Prosthetics Laboratory at the Naval Hospital in Oakland, Calif. The work in the Laboratory has been directed toward the production of prostheses for amputees, and this has been extended to include congenital deficiencies of extremities. These studies are of investigative nature, and when a prosthesis appears to be satisfactory the manufacture is turned over to commercial houses. Nevertheless, new biological structure replacement materials are constantly sought. Of particular importance in this connection is the rehabilitation of the patients. Their pride in the use of the prostheses and in their ability to perform numerous intricate tasks is outstanding.

During World War II, officers at the Naval Medical Research Institute investigated the blast injuries of crew members thrown into the sea by enemy action and exposed to underwater blast when immersed. This had an important bearing on the management of those who were rescued. The armored vest was developed at the Naval Medical Field Research Laboratory at Camp Lejeune and has had significant influence on incidence and types of wounds in the field in Korea. Similarly, the Navy boot is important in preventing frostbite and injury by land mines. The Air Crew Equipment Laboratory and that at Johnsville have studied acceleration and deceleration, the latter of direct importance to surgical treatment. The study of blast effects at the Navy Mine Defense Laboratory will be of surgical significance in the recognition and management of injuries so acquired.

It is not my intention to give the impression that surgeons are interested only in items of direct surgical importance. The new calorimeter at the Naval Medical Research Institute represents the greatest advance in calorimeters in the past half century. The human disorientation device at Pensacola is unique in the study of orientation of pilots. Valuable studies of cholera, brucellosis, typhus fever, amebiasis, and other diseases carried out in the unit in Cairo, Egypt, have led to certain improvements in diagnosis and treatment. Further work on exotic diseases will be conducted in Formosa. Continued investigations of acute upper respiratory disease at Great Lakes, Ill., give promise of prevention of these disorders and such sequels as rheumatic fever and nephritis. At San Francisco, the prevention and treatment of irradiation injury are studied intensively. To detail all the investigations in progress requires more than an editorial. However, enough has been said to indicate that the Medical Department of the Navy is dedicated to "combat readiness" and "success in battle."

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Surgical Teaching and Investigation in the United States Air Force

The United States Air Force Medical Service is now seven years old. Beginning in 1949 the new military medical service was free to examine new ideas and select operational and clinical policies in tune with a rapidly progressing medical science and adaptable to the newer principles of military science exemplified by the Air Force. To bolster this youthful framework, critical attention was paid to the experience of schools, hospitals, and other medical organizations that have been many years in building traditions and reputations. With this heritage from which to draw, the Air Force Medical Service is permitted an unfettered approach to many problems of research and teaching as well as to the practice of surgery. New ideas both from without and within the Air Force can be evaluated and adopted without the resistance of tradition.

To take advantage of the experience of recognized centers of teaching, the Air Force has at present about 180 medical officers in surgical training; approximately 70 civilian universities and hospitals are taking part in the program of training these physicians in the various surgical specialties. This program permits learning and adoption of the best of civilian medicine for the solution of military surgical problems and allows Air Force physicians to be aware of and take part in surgical research and investigation under the leadership of the best and most active teachers and investigators.

To continue the maturation of the surgeons who receive their formal training in the program outlined above, they are, upon completion of their residencies, assigned to surgical positions in various Air Force hospitals. Usually these assignments are planned to permit the young surgeon to work under the guidance of an older, more experienced man. To allow the surgeons' careers to develop to their greatest potential, it is Air Force policy to keep them assigned to their special field. It has been the pleasant experience of many young Air Force surgeons to find that a wealth of surgical material is available to them. This fact, plus the policy of permitting surgeons to attend refresher courses and national professional meetings throughout their careers, results in a continuous and cumulative course of training.

The surgeon who has an interest in research is encouraged to initiate or continue investigation of any problem in which he has become interested. This may be done as part of a large integrated research program at one of the research centers such as the School of Aviation Medicine or may be done as an individual effort supported and encouraged by the medical installation to which he is assigned. An expanded program of teaching and research in surgery and other medical fields is now being introduced into the larger Air Force hospitals.

In summary, it may be said that the Air Force Medical Service has a program of teaching and research that gleans the best from the civilian surgical field, transfers this to the service organization, and continues to nurture the surgical careers of its officers by continued training and experience throughout their careers. Specific plans are now being introduced that will add to this program through the establishment of Air Force centers for teaching, investigation, and surgical care of the sick.

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Healing of Infected Wounds Treated with Human Plasmin and Hyaluronidase

Débridement and Healing of Infected Wounds, Several with Metallic Foreign Bodies

EUGENE E. CLIFFTON, M.D., New York

Enzyme therapy of infected wounds and ulcerating lesions is a rapidly developing field, in which there is great promise. It is said that John Hunter used crude pancreatic enzymes in the treatment of wounds. The maggot treatment of dirty chronic infected wounds and osteomyelitis cavities was undoubtedly effective because of proteolytic enzymes secreted by the maggots.[1] The modern methods of enzyme treatment using purified materials have been developed only in recent years.[2] Papain[3] was used as long ago as the First World War for cleansing of infected burns and dirty wounds but was abandoned because of the severe irritation it caused. It was with streptokinase and streptodornase[4] that the first well-controlled studies of this type of therapy were made.[5-8] Trypsin, a proteolytic enzyme obtained from the pancreas, is a stronger digestive enzyme, which has been used with success in debridement.[9-11] Bovine plasmin (fibrinolysin) has also been reported to be useful in debridement.[12]

Additions to this group of enzymes are being and will be made from time to time. Pancreatic desoxyribonuclease recently has been prepared for clinical use.[13,14]

With the preparation of human plasmin[15,16] (fibrinolysin), an active natural enzyme from human sources has been made available. Previous studies on chronic ulcers[17] and soft-tissue wounds have indicated that this material is very effective in debriding these lesions.[18] Infection was decreased, probably as a result of better drainage and removal of the debris which furnished a good culture medium. Healing time was shortened but not as much as one might wish; therefore another enzyme, hyaluronidase, was added and the combination was found to shorten healing time markedly, in most instances by 50%.[18]

This series of cases is reported because of the difficult nature of the problems presented. All had had strenuous attempts at control by many other methods, including surgical treatment, antibiotics, Dakin's solution, and irrigations, before, usually as a last resort, they were referred for consideration of enzyme treatment.

Materials

1. Plasminogen,* † prepared from human plasma (fraction or -3)

2. Streptokinase-streptodornase (SK-SD),‡ SK, 100,000 units, SD, 20,000 units per vial; each vial dissolved in 10 cc. of distilled water.

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From Andre and Bella Meyer Physiology Laboratory (Enzyme Research Section) of the Sloan Kettering Institute for Cancer Research and the Memorial Center for Cancer and Allied Diseases.

* Furnished by Sharp & Dohme, Division of Merck & Co., Inc., through Drs. R. T. Smith and W. Baumgarten.

† Furnished by Ortho Pharmaceutical Corporation, through Drs. R. V. Chapple and H. O. Singher.

‡ Varidase, Lederle Laboratories Division, American Cyanamid Company.

3. Hyaluronidase (Diffusin),§ 1500 TRU (turbidity reducing units) per vial; dissolved in 10 cc. distilled water.

4. Trypsin,‖ 250 mg. dissolved in 25 cc. of buffer solution.

5. Methylcellulose U. S. P. (Methocel); prepared containing hyaluronidase and at times plasminogen or plasmin.

Methods

The plasminogen was placed in solution buffered at pH 7.6 in a concentration of 0.35 mg/cc.

Ten cubic centimeters of the plasminogen solution was activated with 0.5 to 1.0 cc. of streptokinase-streptodornase. This solution was instilled into the wound with care to reach the depths of the wound, in order to maintain contact with all surfaces of the wound. Later in the course hyaluronidase solution was added to the instillate in some cases or used alone in others. Special techniques of use such as use of methylcellulose or packing the wounds with gauze or fibrin foam soaked in the enzymes, were used where indicated, as described in the case reports.

Results

Nineteen patients have been treated, with excellent results in sixteen and complete healing in fifteen cases.

Five orthopedic patients with infected wounds involving the bone were treated, three with complete success. Two of these had metallic foreign bodies in the infected wounds. One had a large prosthesis replacing the head and neck of the femur; the other, a Moore prosthesis replacing the head.

Case 1.—A 63-year-old white man had a prosthesis inserted to replace the head and neck of his femur, and after a secondary operation for dislocation he developed a severe wound infection. The infection became apparent on the seventh day following the second operation, despite antibiotics, and the wound had to be opened widely. On the following day there was a profuse foul-smelling drainage, and culture showed Staphylococcus aureus and B. proteus. Irrigations with full-strength Dakin's solution four times a day were started immediately. The wound remained wide open, down to the prosthesis, the neck of the femur, and the acetabulum, and actually had enlarged by July 7, 1954, the 17th day after the opening of the wound. There was still spreading necrosis, especially in the fascia at the base of the wound. On July 15, the culture was repeated, showing Proteus, enterococci, Staphylococcus aureus and Pseudomonas aeruginosa (B. pyocyaneus). Throughout this time the patient was also receiving antibiotics as directed by consultants. He was seen on July 30, 1954, thirty-nine days after the onset of the wound infection, when the wound was found to be 12×5 cm. and 12 cm. in depth. There were two sinuses, each about 12 cm. in length, through to the skin above and below the main wound. Prosthesis and bone could be seen in the depths of this wound in addition to the necrotic debris including necrotic tendon and fascia. Instillation of trypsin solution b. i. d. was started, and parenteral antibiotics were discontinued. By the sixth day the wound was beginning to clean up, but there was still much necrotic debris in the base and a great deal of necrotic purulent material could be irrigated out of the sinuses and the depths of the wound at each dressing. The treatment was changed to plasmin, 10 cc. plus hyaluronidase 10 cc. (1500 TRU) and bacitracin 2 cc. (1000 units/cc.). By Aug. 11, five days after plasmin was started, the wound was clean and pink and held only eight cc. On this day the bacitracin was discontinued. The only organism cultured at this time was B. proteus. Nine days later, Aug. 20, fourteen days after plasmin treatment was started, the upper sinus was almost completely closed and it was then impossible to feel the prosthesis with a metal instrument. The entire cavity held only 5 cc. By Aug. 24, after 18 days of plasmin and hyaluronidase treatment, the upper sinus was solidly healed, and from this time hyaluronidase alone was used. By Sept. 13, 37 days after beginning plasmin and hyaluronidase, the lower sinus was completely healed and the main wound held only 2 cc. At this time the depth of the wound was curetted, and absorbable gelatin sponge U. S. P. (Gelfoam) soaked with hyaluronidase was packed into the small residual cavity. Two days later the wound was practically healed except for a small nipple containing a little granulation tissue, and enzyme treatment was discontinued. The cast was removed and the patient was started on active motion, a few days later. By Oct. 14, 1954, the patient was able to walk almost completely across the room. There has been no

§ Furnished by Ortho Pharmaceutical Corporation, through Drs. R. V. Chapple and H. O. Singher.

‖ Trypsin crystalline, The Armour Laboratories.

recurrence of infection in the wound to the present, two years later.

CASE 2.—A 44-year-old white man had a wound infection of four months' duration, despite antibiotics and adequate surgical excision and drainage, following nailing and later replacement of the head with a Moore prosthesis. After excision of a sequestrum and drainage on Aug. 29, 1955 the wound continued to drain about 20 cc. of pus (Staphylococcus aureus) despite chloroazodin (Azochloramid) irrigations and dressings t. i. d. and parenteral tetracycline, U. S. P. (Achromycin). Sixteen days later, Sept. 14, 1955, plasmin was started, and within two days the purulent drainage had ceased, and by Sept. 19, 1955, four days later, the wound was clean and plasmin was discontinued. Hyaluronidase was then used daily and the wound was healed completely by Oct. 3, 1955, after 19 days of treatment with the enzymes.

CASE 3.—A 70-year-old white woman had a fracture of the femur and tibia treated by an open operation, followed by osteomyelitis, in December, 1954. In May, 1955, a saucerization was performed without relief, and a larger saucerization was necessary on June 2, 1955. This had done poorly on the usual treatment. There was residual infection and necrotic debris, including necrotic ligaments and fascia and sinus tracts through the joint space and down to bone, when she was seen in consultation on June 30, 1955. She was treated with trypsin for one week, then liquid plasmin for two weeks. The regimen was then changed to methylcellulose U. S. P. with plasmin plus hyaluronidase. This treatment was continued for one week in the hospital and two weeks at home. At the end of this time, Aug. 1, 1955, the wound was completely healed. It is of particular interest that this patient complained bitterly of pain with the trypsin treatments and the granulations were a deep angry red, whereas with the plasmin she had no discomfort and the granulations were pink.

Cases 4 and 5 were failures so far as complete healing was concerned. Both were patients with narrow fibrotic sinuses, of over six months' duration in one case and over five years' duration in the other. The latter also had a metallic plate. In both instances, the drainage was rapidly diminished to practically nil, and indeed the wounds seemed almost healed. However, in both cases the wounds subsequently reopened. Both have been reoperated upon and were found to have a very fibrous sinus tract leading down, in Case 4, to a mere shell of femoral head filled with granulation tissue and, in Case 5, to a granulation-filled cavity surrounding the metal plate in the mid-femur.

CASE 6.—A 73-year-old white man had a complete gangrene of toes 1, 2, and 3 with partial gangrene of the fourth toe and the foot at the base of the toes, of several months' duration. A transtarsal amputation was attempted, with little hope of success. By the eighth postoperative day necrotic tissue including tendons was present and there was infection with bare bone in two places. The open wound increased in size in the next three days despite antibiotics. Plasmin was started on this day (the 11th postoperative day), and the antibiotics were discontinued. Within three days the wound was becoming clean and the tendons were beginning to be debrided. From this time plasmin solution was used for 10 minutes followed by methycellulose gel containing hyaluronidase. The wound was completely debrided and granulating and the medial one-half had healed with good skin covering by the 13th day of treatment. On the 14th day pinch grafts were placed on the remaining clean granulating base. Hyaluronidase liquid was used for the dressing at operation. Daily dressings with hyaluronidase were used until Oct. 15, 1955, the 35th day after the original operation, the 23rd day after beginning enzyme treatment, when the area was completely healed. It has remained healed, and the patient is walking with a special shoe one year later.

Patients with Draining Gastrointestinal Fistulae and Abdominal Wound Infections. These patients were all seriously ill with fistulae and infections complicating major abdominal surgery.

CASE 7.—A 58-year-old white man had a subtotal gastrectomy and inversion of a duodenal diverticulum on Dec. 3, 1953. A wound infection occurred which took a month to heal. Following this he had a recurrent wound infection with a draining fistula into the duodenum first visualized on Feb. 24, 1955. He had reoperations on March 1 in the R. U. Q. and March 17 in the L. U. Q., following which drainage continued until April 20. On May 24 he was readmitted with recurrence and he was reexplored in another attempt to close the fistula. The large transverse wound was packed open. A fistula was present with a large intra-abdominal abscess cavity. Continuous Dakin's

irrigations through four catheters were begun on June 24, and on the fifth day following this bile was found to be draining from the lower end of the wound. On June 28 irrigations were changed to streptokinase-streptodornase, hyaluronidase, and bacitracin. Because there was no further improvement in the wound, he was started on plasmin, hyaluronidase, and bacitracin five days later. Five days after this the wounds were clean with pink granulations. The small sinus tract in the right side of the wound was proved to open into the abdominal cavity by a long sinus tract under the undermined flap. At x-ray visualization on July 12, 1954, the 14th day of treatment, the sodium acetrizoate (Urokon) dropped into the free peritoneal cavity and pooled in the pelvic region and on inversion flowed up over the liver and pooled under the diaphragm. The patient had a severe reaction to the sodium acetrizoate in the free abdominal cavity, although he never had had any reaction to the plasmin or hyaluronidase, in the free peritoneal cavity. He was continued on the plasmin and hyaluronidase, with slow healing until July 21. At this time there was no drainage of bile and the wounds were so clean that plasmin was discontinued, but hyaluronidase was continued. The T-tube was removed on July 22. On Aug. 2, 1954, a sodium acetrizoate visualization of the sinuses was attempted, and after strong pressure the catheter was forced into the gastrointestinal tract and the x-ray showed filling of the small bowel. Packing with hyaluronidase was continued and the patient was discharged on Aug. 5, 1954, the 32nd day of enzyme treatment. As an outpatient, he continued to have his dressings changed every two days, with irrigations and then packing of the wound with absorbable gelatin sponge soaked in hyaluronidase, and by Aug. 18, 1954, the 45th day of the enzyme treatment, the wounds were healed except for one sinus about 2 cm. in depth and 4 mm. in diameter. The hyaluronidase was discontinued, and the wounds were healed completely by Sept. 22, 1954, and have remained so to September, 1956 (two years).

Case 8.—A 46-year-old white man had an anterior resection of the lower sigmoid with a transverse colostomy on Dec. 16, 1953. He developed a perforation at the anastomosis with a huge retroperitoneal abscess. It was necessary to incise and drain the abscess in the loin well above the crest of the ilium. Through-and-through drainage was obtained, but despite repeated irrigations and parenteral antibiotics the thick purulent drainage continued, becoming more hemorrhagic as time went on. The opening in the rectal suture line easily admitted two fingers. A daily temperature rise to over 100 F continued. On Jan. 20, fifteen days after the incision and drainage, iodized oil U. S. P. (Lipiodol) injection of the sinus tract was made, through which the rectum could be filled with iodized oil from above. Two days later, Jan. 22, 1954, instillation of streptokinase-streptodornase, hyaluronidase, and bacitracin was begun. The drainage improved, becoming thinner but still purulent and bloody, and after the fourth day the irrigations were changed to plasmin with hyaluronidase and bacitracin solution. The temperature fell to normal on the second day, and the abscess was cleansed very rapidly. By Feb. 7, 1954, the 15th day after beginning enzyme treatment, he was discharged with a completely clean wound which held approximately 5 cc. in the sinus tracts rather than the more than 50 cc. which it held at the beginning. He was followed on an outpatient basis with occasional saline irrigations, and the wounds in the loin and in the rectum were completely healed by Feb. 14, or 22 days after the beginning of treatment, and one month later his colostomy was closed without any further difficulty. At last follow-up, one year later, he was well.

Cases 9, 10, and 11. Three cases of simple ileal fistula without wound infection were treated with hyaluronidase in methylcellulose gel. All fistulae healed within one week and remained closed. One had been open for 3 weeks, one for 10 days, and the other for 4 weeks without evidence of improvement.

Subphrenic Abscesses with Long Sinus Tracts.—Two patients who had subphrenic abscesses with poor drainage through long sinus tracts were treated with success.

Case 12.—A 63-year-old white woman had a subphrenic abscess following a colon resection which had drained spontaneously, but very poorly, through a long sinus. This drained thick pus sporadically, and she continued to have a high fever. Irrigation was virtually impossible, and an operation was considered but contraindicated because of her poor condition. Plasmin was instilled with difficulty the first day because the catheter could not be inserted into the cavity. The next day, however, the catheter dropped in with ease and the cavity was found to contain more than 30 cc. of thick pus and debris. Plasmin was instilled daily. After five days the patient's temperature was normal and the drainage was thin and free, and

after 10 days drainage was minimal. Hyaluronidase was instilled after this, and 20 days later (30 days after treatment was started) the abscess and sinus were completely healed.

CASE 13.—A 41-year-old white woman was transferred from another hospital after resection of a carcinoma of the colon and the left lobe of the liver, Dec. 15, 1954. Because of residual disease, she was admitted to Memorial Hospital for radiation therapy. During her postoperative course she developed an abscess in the left upper quadrant, which had been drained, and a fistula with a narrow opening was present which drained brown foul-smelling bloody material. The drainage had been unimproved with antibiotics, cortisone, and frequent irrigations. There was evidence of blockage with fluctuance and a mass increasing in size in the left upper quadrant and extending over to the right upper quadrant. She was referred for enzyme treatment on the 30th day after admission to Memorial Hospital, about seven weeks after the onset of her infection. An iodized oil study showed a large intra-abdominal cavity with a narrow fistulous tract connecting with the skin. On the first day it was impossible to get a catheter into the sinus; therefore, an adapter was inserted into the sinus and plasmin (5 cc.) was forced into the abscess. The next day 10 cc. was injected without difficulty, and on the third day it was possible to get a No. 20 catheter into the abscess; at this time 20 cc. of plasmin could be placed in the cavity without pain or discomfort. An x-ray again on the third day after plasmin treatment was begun showed a large elongated cavity. Following this there was slow improvement in the cavity, with a decrease in size, obvious by the amount of plasmin that could be instilled. By the 10th day only 6 cc. could be instilled without pressure and the fluid was beginning to thin out. On the 13th day after the beginning of treatment it was obvious that a new pocket had been opened by the plasmin, since there was drainage of a large quantity of purulent material and the cavity now held more than 10 cc. of plasmin. Following this, improvement was rapid. The abdominal swelling had decreased in size, and there was no longer tenderness or pain present; by the 20th day following the onset of treatment, she was discharged with a very small (2 cc.) sinus in the skin and subcutaneous tissue only, which healed after the patient was discharged from the hospital.

Chronic Sinuses and Abscess Cavities in Subcutaneous Tissue.—Several cases of chronic sinuses which responded well to enzyme treatment have been reported previously.[18] Only three new cases are included in this group. Other uncomplicated cases will not be reported. One of the three cases in this series was the oldest and had a very poor prognosis for healing.

CASE 14.—A 26-year-old Negro female employee was admitted in October, 1954, with a history of draining sinuses in the posterior neck, of four years' duration. She had previously had an incision and drainage of abscesses plus antibiotic treatment on several occasions in other hospitals and in Bellevue. In February, 1954, she had been admitted with a large brawny indurated area, with fluctuation plus several draining sinus tracts. This was incised and drained, and she was given a long course of chlortetracycline (Aureomycin) hydrochloride. The cultures were positive for Staphylococcus albus and aureus, and there was one positive culture for tubercle bacilli. She was treated for three months with isoniazid and then streptomycin and aminosalicylic acid (PAS) for three months without change in the sinuses. In October she was readmitted with other fluctuant areas and after incision was treated with oxytetracycline (Terramycin). A trial of enzymes was accepted, before a massive resection of the entire area with grafting was undertaken.

On Nov. 5, 1954, trypsin instillations into the sinuses were begun, with use of polyethylene catheters. Trypsin was continued for six days, and then plasmin was instilled daily for eight days. By this time the drainage was clear and minimal. Hyaluronidase was then started and continued for almost six weeks, when the sinuses were completely healed. Not only was there healing but the skin and subcutaneous tissues were themselves softer, more pliable, and more freely movable than at any period of observation at Bellevue. She has remained healed for over one year.

The second case of this group (Case 15) had a perineal sinus which had been present for two years following abdominoperineal total colectomy for colitis. She had been reoperated upon and curetted, with minimal evidence of healing after six weeks, and then was treated with plasmin and hyaluronidase for three weeks, with complete healing.

The third case (Case 16), a white man, was a complete failure. This patient was a paraplegic with a known sinus in the

buttock region of at least seven years' duration, which had reopened eight months before. It was impossible to inject more than 5 cc. of solution without producing discomfort, chills, and fever. At operation he was found to have an old, thick-walled cavity, 20 cm. in diameter and filled with granulations. It is obvious that contact was not obtained by the enzymes.

A fourth case (Case 17) with sinus tracts in the neck due to acid-fast bacilli was treated for only 10 days during hospitalization until a definite diagnosis was made. Her sinuses stopped draining pus in this time and were apparently beginning to heal. They subsequently healed completely on treatment with specific medication.

Postoperative Wound Infections.—Only two patients with complicated superficial chronic wound infections are of sufficient interest to be considered here, although many others have been treated with success as early cases.

The first of these (Case 18) was of three months' duration, during which time the patient had been treated by antibiotics, heat, and Dakin's solution without improvement. This case is of importance only to point one lesson, that care must be taken with other medications. While she was in the hospital her wound was dressed by the treatment room nurses, who as a routine used hydrogen peroxide spray to clean the wound before applying the plasmin. It is not surprising that little effect was obtained, since the free oxygen would destroy the enzyme. When she went home, however, and did not have the advantage of this deluxe service, her wound healed in two weeks with the use of plasmin and hyaluronidase in methylcellulose gel.

Case 19 had had three operations ending in nephrectomy for ureteral calculus and infected kidney. There had been repeated hemorrhages of severe nature from this infected wound. Despite heavy doses of antibiotics he continued to have a spiking fever and had lost 50 lb. (22.5 kg.). Despite the hemorrhagic drainage all antibiotics were stopped and treatment with plasmin was started. Within three days the temperature was normal, and within seven days the wound was clean and beginning to heal. An obvious connection with the ureteral stump was eventually proved. This patient's wound had healed down to a narrow sinus with minimal drainage owing to retention of an umbilical tape known to be used in addition to heavy silk for a mass ligation of the kidney pelvis. He regained his weight and returned to his regular practice as a physician. Subsequently the umbilical tape was removed and the wound healed completely and has remained healed.

Comment

It is obvious that a group of cases such as this cannot be treated statistically. It is equally apparent that they acted as their own controls, since the majority had had the advantage of many of the commonly used treatments without significant improvement. Most cases were of long duration without healing, or were increasing in severity at the time enzyme treatment was started.

The healing of infected wounds in the presence of metallic foreign bodies is itself so unusual as to warrant comment. Other patients similar to the patient with the hip prosthesis have had to have removal of the metal head, with obvious crippling and, indeed, in some instances amputation. Case 2 healed with a smaller prosthesis in place.

The relative effectiveness of the proteolytic enzymes used also deserves some comments. Although trypsin is a much stronger enzyme than the others, it suffers by comparison with plasmin because of its short-lived effect and also because of its irritative effect—shown particularly in Case 3 by the excessive and very red granulations and by the pain reaction in this patient and other patients with radiation ulceration not reported here. Another disadvantage is the occasional toxic reaction due to absorption of the enzyme or protein breakdown products.[19] It has also been reported that trypsin

digests partially viable tissue as well as necrotic debris and so has produced increase in size of lesions rather than a decrease. It must also be remembered that an inhibitor (antitrypsin) is present in the serum and in the exudates, which rapidly increases in concentration after the use of trypsin.[20] This explains the need for increasing the concentration of enzyme on successive days. It still remains a useful enzyme, especially where protein debris other than fibrin is to be digested and where it can be used frequently without pain.

Streptokinase-Streptodornase is effective primarily as an activator and depends on the plasminogen in the wound exudates;[4] it suffers by comparison with other healing agents because knowledge is lacking concerning the exact amount of enzyme being used. It would seem to be particularly useful in fresh wounds containing blood, plasma, or transudates.[4] Occasional pyrogenic reactions may be expected.[21] It was not found to be as effective as plasmin in the two cases (Cases 7 and 8) in which it was used in this series. It should be noted that the amount of Streptokinase-Streptodornase used in activating the plasminogen in these cases was much less than would be necessary to produce activity. Inhibitors to Streptokinase are also present in many persons who have had streptococcal infections and are developed following treatment with Streptokinase-Streptodornase.[23]

The efficacy of hyaluronidase in speeding healing in these old chronic wounds and in the few fresh ones is largely empiric, but it rests on some theoretical basis. Hyaluronidase may act by its effect on the intracellular ground substance, permitting increased diffusion of oxygen and nutrients and so improving healing. There was no hesitation to use hyaluronidase even in the presence of infection because of our previous experience. In fact, infection was not spread in these cases, despite contrary theory, and indeed with the proteolytic enzymes infections were frequently improved even though antibiotics were discontinued. Apparently this is because of the removal of the culture medium by debridement, allowing the tissues to drain freely into the wound rather than by pressure into the systemic space. There have been no reactions to the enzymes used in these cases.

In our hands the best enzyme combination at present would seem to be plasmin in very dirty wounds or plasmin and hyaluronidase in wounds with less necrotic debris or in wounds once they are partially debrided. After the wounds become clean and are lined with pink granulations, hyaluronidase alone should be used. Where long sinuses are present the liquid should be used, but in larger open wounds or shallow wounds the enzymes can be used satisfactorily in methylcellulose gel. Where denser debris is present, trypsin may be most effective for a few days.

Other enzymes will certainly be developed and made available. At present desoxyribonuclease derived from pancreas (pancreatic Dornase) is especially valuable for tracheobronchial secretions and is also effective in wounds with necrotic cellular debris.

Summary

Proteolytic enzymes, especially human plasmin, are useful in hastening the debridement of infected wounds. In conjunction with hyaluronidase, healing is hastened and has been consummated even in the presence of large metallic foreign bodies, osteomylitis, and necrotic tendons and fascia.

Special care and knowledge is necessary in using enzyme therapy because of the simple conditions which may cause inactivation of the enzymes.

Fear that infections will be spread by enzyme therapy is unwarranted, according to this experience.

There have been no undesirable side-reactions with human plasmin or hyaluronidase.

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Ectopic Urethral Anus in Rectourethral Fistula

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Any genitourinary defect of embryologic origin should be studied meticulously for new information contributing to an understanding of the anomalies. Such studies are of value not only because of their simple addition to factual knowledge but also because of possible use of the acquired information in planning new surgical procedures and in evaluating the results of therapy. The case upon which this report is based is of particular interest in this respect, since it is the first proved example of an ectopic prostatic urethral anus.

Report of a Case

A white boy was born after seven months normal gestation. Thoracotomy was done the same day because of esophageal atresia. The child died a few hours afterward. At postmortem examination auricular and ventricular cardiac septal defects, a patent ductus arteriosus, and a fourth-lumbar hemivertebra were found, in addition to the esophageal anomaly.

There was an imperforate anus. The rectum terminated in a blind pouch 1.5 cm. from the perineal skin surface. No fistulous tract leading from the rectum was identified grossly. The areas consisting of terminal rectum, bladder, prostate, and seminal vesicles were removed en bloc. This tissue block was then bisected, the halves were embedded in paraffin, and skipped serial sections were made. Reconstructions were made from the sections (Fig. 1). There were multiple minute fistulae leading from the terminal end of the rectum toward the prostate and prostatic urethra (Fig. 2, *A*). By reconstruction, it became evident that some of these fistulae opened into glandular spaces that, in turn, opened into a larger sac lined by squamous epithelium. This sac communicated with the prostatic urethra. The glandular spaces were lined by a cuboidal epithelium that resembled the lining of prostatic glands (Fig. 2, *A* and *B*). It is impossible to say whether this is rectal or genitourinary epithelium. The squamous sac extended from the urethra to the posterior portion of the prostate, and a portion of the well-developed squamous epithelium covered the urethra immediately adjacent to the sac opening (Fig. 2, *C*). This squamous sac was thought not to be prostatic utricle because of its size, inferior location, fistulous opening into the rectum, and lack of similarity of its epithelium to that of prostatic utricles. The urethral origin at the bladder was distorted by ridges in the ostial wall. The prostatic urethra was dilated and of irregular shape in the region of the verumontanum. There was a dimple in the muscular tissue of the perineum below the terminal rectal pouch and prostate, indicating that genesis of the perineal muscle may proceed normally even in the presence of epithelial abnormalities.

Fig. 1.—Artist's drawing of lucite reconstruction model made from tissue sections. The rectum is at left, urinary bladder above, and prostatic region at lower right. Multiple fistulae extend from the lower end of the rectum to join a large, rounded (squamous) sac, which, in turn, opens into the prostatic urethra.

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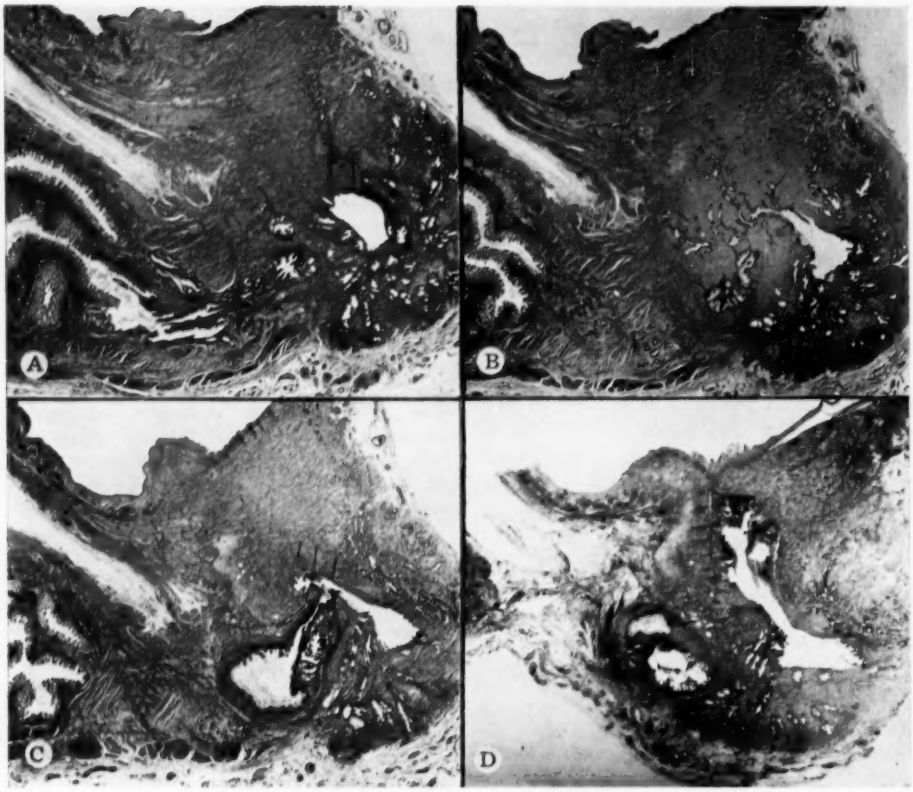

Fig. 2.—Photomicrographs of successive levels of tissue block of rectourethral anomaly. Urinary bladder is space at top, rectum on the left, and prostatic region on the right. *A*, section showing multiple fistulae from rectum extending toward large glands behind prostatic urethra; reduced from mag. × 9. *B*, section at deeper level than *A*, showing beginning of squamous-lined sac with large glands that connect with rectal fistula opening into superior right portion of squamous sac; reduced from mag. × 9. *C*, section at deeper level than *B*, with large cross section of squamous sac opening into urethra; reduced from mag. × 9. *D*, deeper section than *C*, showing extreme lateral extension of squamous sac, lying just above seminal vesicle; reduced from mag. × 9.

Interpretation and Comment

The provocative feature of this examination is the finding of a well-developed squamous epithelial covering of the posterior surface of the prostatic urethra and adjoining squamous epithelial sac. This defect is even more unique, since the urethral terminus of the rectourethral fistula is the squamous-cell-lined sac. These features demand careful interpretation.

There is currently no unanimity of concept concerning defective organogenesis of the rectum and anus. Six different ideas have been proposed.[5,9,11-16] These postulates may be divided into two principal categories. The first assumes that the active differentiating force is mesenchymal and that these tissues grow and obliterate epithelial elements. The second general concept is that epithelial proliferations and migrations are the active force and proceed together with supportive mesenchyme. The remainder of the mesenchyme passively fills in the space between epithelial structures. Rectourethral fistulae are said never to occur in the presence of a normal rectum,[6] a fact that supports the theory that active epithelial proliferation is the most

important factor in rectourinary fistulae. If the defect were due solely to difficulties in mesenchymal proliferation, it would seem that there would be some cases with a normal rectum but with septal fistulae. Therefore, it is this last postulate of dominant epithelial forces that seems most logical and with which our findings correlate most closely.

It is from this particular case that we derive a new concept of defective organogenesis of rectourethral fistulae. This concept is based upon the important finding of an islet of squamous cells adjacent to the prostatic urethra. The concept can best be grasped by postulating the sequence of events that must have occurred as the embryo developed. In the seventh week, the urorectal septum was formed by multiple ingrowths of proliferating rectal epithelium with its mesenchymal sheath. Epithelium at the inferior and posterior part of the urorectal septum then proliferated to form the proctodeum, which remained connected or attracted to the urogenital tube and the opening of the Müllerian duct (Fig. 4,*D* and *E*). Because of this surface attachment, the surrounding proliferating mesenchyme was unable to separate the proctodeum and urogenital tube but instead proliferated caudally to it. It formed the perineum and joined with mesenchyme that had closed the tail gut, isolating the rectal part of the cloaca internally at some distance from the perineal surface. Simultaneously, the epithelial-mesenchyme mass from the high rectum continued to proliferate downward. A positive attractive force was exerted upon this mass by the proctodeum, which was still attached to the urogenital tube. The terminal rectal buds, which lined the posterior cloacal space, joined the urethral proctodeum and united with it, thus forming the fistula (Fig. 4,*F* and *G*). The urogenital tube was then isolated inward by proliferating mesenchyme and the urethra was formed distal to it. At seven weeks the proctodeum and urogenital opening are immediately adjacent, and it is the persistence of this adjoining state which accounts for the defect.

This concept of a urethral focus of squamous cells representing an ectopic anus is supported by other reports of ectopic anus in somewhat similar sites.[3,17,19-21] Young[18] reported a case of anterior ectopic perineal anal orifice, rectourethral fistula, and hypospadias. Another case of anterior perineal ectopic anus with a rectourethral fistula opening in the perineum at the base of the penis and hypospadias is reported by Denis Browne.[6]

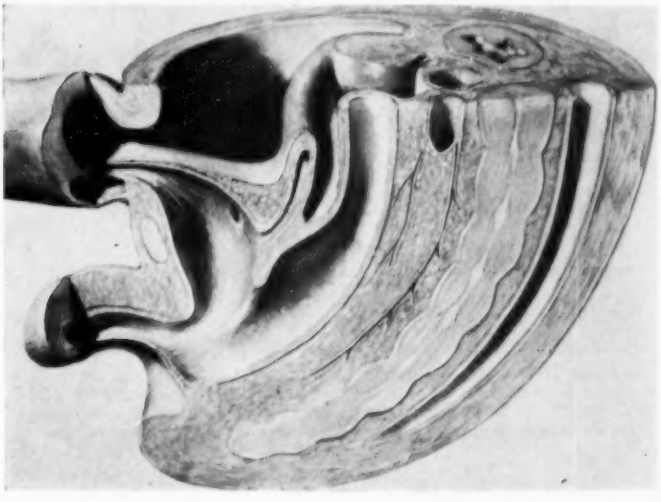

Fig. 3.—Artist's schematic drawing of normal urogenital region in embryo of 7 weeks. Both normal and abnormal sequences of Fig. 4 follow this stage.

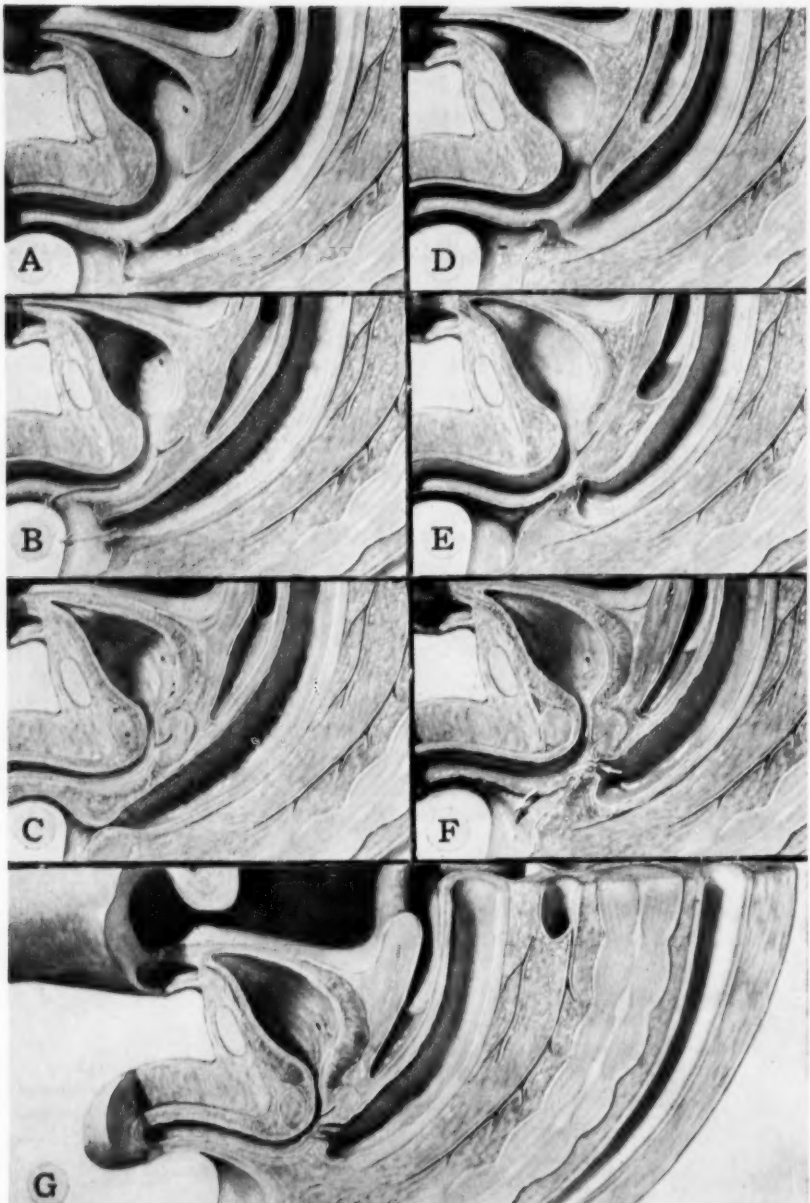

Fig. 4.—Normal and abnormal development of urorectal septum, rectum, anus, and urethra between the 7th and 12th weeks of embryonic life. *A*, *B*, and *C* are the normal sequence of events, and *D*, *E*, *F*, and *G* are the postulated sequence of events that occurred in our case of rectourethral fistula. Arrows indicate points of rupture of urogenital and anal membranes.

It may be that many congenital recto-urethral fistulae have their origin in the manner described above. However, prior to the fortuitous demonstration of a mass of squamous epithelium covering the posterior portion of the prostatic urethra in this case, histologic proof for the hypothesis of rectourethral fistula due to ectopic anus has been lacking.

Summary

The pathologic anatomy of a case of previously unreported ectopic prostatic urethral anus is described.

Evidence is presented that development of rectourethral fistulae by defects in the mesenchyme of the urorectal septum is not the only possible mechanism by which such fistulae develop. In this case it is more likely that anterior displacement of the squamous epithelial anus to the urethra occurred, with subsequent union of the ectopic anus to fistulous epithelial processes from the rectum.

Mr. William B. McNett made the reconstruction and drawings for Figures 1, 3, and 4.

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Acute Hemorrhagic Pancreatitis

An Experiment Method of Its Production and the Effect of Vagotomy

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I. Introduction

Inflammatory disease of the pancreas is characterized by edema, hemorrhage, necrosis, and suppuration. The gross picture of acute hemorrhagic pancreatitis is accompanied by intraperitoneal accumulation of blood, fat necrosis, and localized adhesions. Inflammatory disease of the pancreas runs the gamut from mild interstitial inflammation to diffuse fibrosis, depending on the duration and severity of the initial insult. The multiple forms of therapy advocated in this disease bespeak the lack of agreement on its basic pathogenesis. There is a good indication for reexamination of this disease in the laboratory animal. It is the purpose of this study (*a*) to describe a method of consistently producing acute hemorrhagic pancreatitis in the dog and (*b*) to evaluate the results of bilateral subdiaphragmatic vagotomy as a definitive method of treatment.

The present day concept of treatment in the acute phase of primary hemorrhagic pancreatitis involves primarily the application of conservative medical management. This treatment consists of relief of pain with sedatives and narcotics, splanchnic nerve blocks, prolonged gastric suction, large doses of vagal blocking drugs, restoration of blood volume, correction of fluid and electrolyte imbalance, and antibiotics.[16] Surgical intervention is indicated in the following conditions: (*a*) if the diagnosis is still in doubt; (*b*) in the presence of jaundice of the obstructive type; (*c*) lack of response to conservative treatment; (*d*) the presence of an abdominal mass, and (*e*) when there are signs of spreading peritonitis. "The chief argument offered against early surgery in acute pancreatitis is the lower mortality rate with the present day non-operative than previous operative treatment, but a better contraindication is the lack of agreement on what specific surgical procedure to apply."[1]

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II. The Theoretical Basis for Vagotomy in Acute Pancreatitis

The application of vagotomy for the treatment of acute pancreatitis is based in theory upon the following data. The vagus nerve when stimulated renders a pancreatic secretion rich in ferments. This action is annulled by atropine at the affector cell level. The vagus nerve controls to a large measure the pancreatic secretion of trypsin, lipase, and amylase. A certain degree of independent visceral autonomic reflex activity exists and can be carried out by the intrinsic (Meissner and Auerbach) plexuses of the intestine; there is no anatomical basis for this as far as the pancreas is concerned. The only nerve supply that governs the character of the pancreatic secretion is that of the vagus nerve. Division of the vagi should abolish the afferent as well as the efferent visceral nerve impulses. Gastric hydrochloric acid when coming in contact with the duodenal mucosa stimulates the formation of the hormones secretin and pancreozymin. Secretin stimulates an external pancreatic secretion high in fluid content and bicarbonate. Pancreozymin governs the secretion of pancreatic ferments; therefore, the vagus nerve does not entirely control the pancreatic ferment secretion.[2,3] In acute pancreatitis basic

therapy usually includes parasympathetic nervous system blocking agents; the agents used are atropine, methantheline (Banthine), and propantheline (Pro-Banthine).[4,13] Insulin hypoglycemia in man results in vagal stimulation producing a fluid in which the total volume is low and the amylase content is high as compared to response to secretin. In vagotomized patients insulin hypoglycemia does not stimulate pancreatic secretion as it does with intact vagi, yet the pancreatic response to secretin in such patients is entirely normal.[6] Vagotomy can prevent ampullary and pancreatic duct system spasm of psychogenic origin, and reduce gastric hydrochloric acid and therefore reduce the output of secretin.[11] Reduction of enzyme production, especially trypsin, should decrease the amount of local tissue destruction. In patients with vagotomy as compared to normal persons and patients with sympathectomies, a decrease of almost two thirds in external pancreatic secretion of enzyme output and total volume [12] has been noted. Gastric aspiration and anticholinergic drugs have been used in an effort to reduce gastric hydrochloric acid and lessen the voluminous pancreatic secretions which may be produced in acute pancreatitis. It has been demonstrated experimentally that when methantheline is administered to animals that have pancreatic duct ligation plus bile and trypsin intraductal administration, the mortality rate of acute pancreatitis so induced decreased from 70% to 30%.[14]

III. Mechanisms in the Pathogenesis of Acute Pancreatitis

Acute pancreatic necrosis can be caused by several mechanisms: (*a*) bile introduction under pressure into the pancreatic duct system; (*b*) infection of the pancreas via the lymphatics, ducts, or blood stream; (*c*) direct trauma to the pancreas, and (*d*) vascular injury such as embolism and thrombosis. These are the principal etiological factors stressed in the literature.[5] Additional theoretical mechanisms in which acute pancreatitis can result are (*e*) a Schwartzman phenomenon reaction in which a sensitizing dose can be injected into the pancreas followed by an intravenous dose of the immune body toxin 24 hours later; acute pancreatitis will occur in the area of the first injection,[7] and (*f*) experimental animals can be sensitized intravenously with horse serum and 20 days later another small injection made into a pancreatico-duodenal vein; this will result in a parenchymatous hemorrhage of the pancreas; this is a form of Arthus' phenomenon.[10]

Arbitrarily this experiment has been based on four factors considered necessary to produce acute hemorrhagic pancreatitis. These factors are bile, trypsin, an alkaline solution of an optimum pH, and duct rupture. By itself, bile injection under pressure will usually cause local edema. Pancreatic juice injection which contains trypsin will usually result in a vascular necrosis. The typical fat necrosis and vascular necrosis seen in acute pancreatitis are due to steapsin (lipase) and trypsin and can come about only if they are external to the pancreatic ducts and the intestinal lumen. Bile added to trypsinogen will activate it into trypsin in a manner similar to enterokinase.[8] The optimum pH for the action of trypsin is 7.1.

The present concept of the pathogenesis of acute hemorrhagic pancreatitis involves the presence of a pancreatic duct obstruction, preventing the outflow of an actively secreting gland. This results in rupture of the duct system and extrusion into the pancreatic parenchyma of the pancreatic ferments. The tryptic ferment comes in contact with the arterioles and venules and causes a necrosis of the walls of these vessels with a resultant localized hemorrhage. Fat necrosis occurs in areas where pancreatic lipase comes in contact with adipose tissue. Since the basic abnormality appears to be the extraductal liberation of trypsin, plus the latter's action on the blood vessels, the manner of inhibiting this reaction would involve (*a*) decreasing the amount of trypsin formed by the pancreas; (*b*) containing the area of damage caused by trypsin; (*c*) neutralizing trypsin

action chemically, or (*d*) removing the entire total pancreatic tissue which forms trypsin. A method to decrease the trypsin output of the pancreas could logically include vagus nerve division.

IV. Material and Methods

Twenty mongrel dogs were used, each weighing 25 lb. (11.34 kg.) or more. The experimental animals were consecutive and continuous as to their choice. No dog once chosen was disqualified for any reason. In ten dogs the experimental method for producing pancreatitis was performed. In ten additional animals bilateral subdiaphragmatic vagotomy was performed at the same time as the initial production of experimental pancreatitis. The completeness of the vagotomies was subsequently verified at autopsy.

The following method was used to produce experimentally acute hemorrhagic pancreatitis in the dog. Under morphine and nembutal anesthesia a midline abdominal cavity exposure was made from the xyphoid to just below the umbilicus. The gallbladder was mobilized and 10 cc. of bile was withdrawn from it; the small puncture hole in the gallbladder was ligated with a single suture. The free lying duodenum (descending loop) was mobilized and brought to the level of the incision along with the vertical tail of the pancreas. The large accessory duct was identified external to the duodenum just as it left the pancreatic tissue proper. Approximately 1 cm. of the duct was mobilized and ligated distally (at its juncture with the duodenum). A small aperture was made into the pancreatic duct and a polythene tube (which had a lumen that fitted over a 19-gauge hypodermic needle) was introduced into the pancreatic duct system to a distance of approximately 3 to 5 cm. A second ligature held the tubing snugly adapted to the wall of the duct. A mixture of 10 cc. of the bile plus crystalline trypsin, 10,000 units in 5 cc. of buffered trypsin diluent, were injected into the duct system under moderate unmeasured pressure.* Following the injection the polythene tube was withdrawn and the pancreatic duct ligated proximally. Subsequently it was always noted that the pancreas turned a nutmeg-brown color indicating the exudation outside of the small pancreatic ductules of the bile and trypsin solution. In 15 minutes this discoloration became hemorrhagic in character. At this time, if indicated, the subdiaphragmatic vagotomy was performed, in which the ventral and dorsal vagi rami were identified, mobilized, doubly clamped, and divided. The nerve endings were ligated proximally and distally and the clamps removed. The dog's abdomen was then closed with interrupted through and through nonabsorbable vertical mattress sutures. In no instance were antibiotics used.

Following this procedure the animal was observed at almost daily intervals in which blood was drawn for serum amylase [9] and blood sugar determinations, and blood smears were performed for the white blood cell differential count. It was considered that the serum amylase determinations would indicate the degree of pancreatic damage. The blood sugar determinations were made as collateral data which might indicate further destruction of the pancreas involving the islets. The severity of the inflammation was followed with differential white counts, although it is admitted that total white cell counts would have been also desirable. These data were then plotted against the time interval depending on the survival of the animals.

* The trypsin solution contained a highly purified crystalline trypsin (Tryptar, Armour Laboratories, Chicago) derived from mammalian pancreas glands. It is stable in the dry form, but when placed with a crystalline trypsin diluent, 75% of the proteolytic activity is dissipated over a period of three hours. Its effective range is pH 5-8. Crystalline trypsin diluent is buffered at pH 7.1. It is prepared by dissolving anhydrous dibasic sodium phosphate, 6.6 mg. per cc. and anhydrous monobasic potassium phosphate, 2.7 mg. per cc. in water for injection.

V. Results

In ten animals in which vagotomy was not done only three survived, resulting in a mortality rate at the end of 24 to 48 hours of 70% for the experimental procedure. In the ten animals in which vagotomy was performed only one survived, resulting in a mortality rate of 90% for the experimental procedure plus vagotomy. The four dogs that survived were killed while in good health at the end of 30 days. All animals were autopsied and the gross descriptions were tabulated. Histologic sections were taken of the pancreas, spleen, liver, omentum, and in selected instances the kidneys. It was noted that in every procedure, except in the four animals that survived, there resulted pancreatic hemorrhage and/or necrosis associated with intraperitoneal blood accumulation and fat necrosis. In the four animals that survived the pancreas appeared shrunken and fibrotic and associated with peripancreatic and periduodenal-omental adhesions.

There was a gool correlation between the onset of pancreatitic inflammation and the white blood cell differential count. Serum amylase levels (Krautman method †) showed a primary rise plus a late secondary rise in the survival group; this may have indicated additional pancreatic damage. As a general rule serum amylase levels did not correlate well with the onset of pancreatic inflammation when the entire group of twenty dogs was reviewed. Blood glucose levels in the four survivors remained constant; microscopic sections of the fibrotic pancreases showed intact islets of Langerhans.

Microscopic studies disclosed that, in all nonsurviving animals (i. e., wherein death occurred within 24-72 hours), the pancreatic tissues were hemorrhagic and necrotic; the intra-abdominal fatty tissues disclosed fat necrosis. In one particular instance there was complete loss of pancreatic tissue architecture. Renal tissue in acute hemorrhagic pancreatitis consistently demonstrated intralobular linear infiltration with round cells, characteristic of pyelonephritis; in one instance marked tubular degeneration was evident. In the surviving animals the pancreatic tissues were markedly infiltrated and replaced by dense fibrous tissue, which grossly cut with the consistency of an unripe pear. In acute hemorrhagic pancreatitis, the most consistent hepatic lesion was an area of focal necrosis surrounded by inflammatory round cells; in one instance of fibrotic pancreatitis, the hepatic tissue cells demonstrated a diffuse vacuolated appearance.

† Normal-average serum amylase determinations for the Krautman method are 70-160 units/100 cc. of blood serum, 189-300 units indicating acute pancreatitis in the human; normal serum amylase levels in the dog have been quoted as ten times those of human.[18]

VI. Conclusions

A method of consistently producing acute pancreatitis in dogs has been presented. This method embodies the present concept of a pathogenesis of acute hemorrhagic pancreatitis. Vagotomy, when used in an effort to reduce the enzyme production of the pancreas and thereby lessen the inflammation and tissue destruction, does not affect the severity of acute pancreatitis at the time of its inception. Pancreatitis, therefore, must be a local process that, once initiated, is uninfluenced by the parasympathetic nerves which supply pancreatic parenchyma. The use of anticholinergic drugs for clinical cases of acute pancreatitis must aid in recovery not by influencing the pancreatic enzyme output directly through the vagus nerve, but by decreasing peristalsis (and therefore vomiting), by depressing the hydrochloric acid-secretin mechanism for pancreatic external secretion, and by acting perhaps as mild sedatives.

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Myocardial Revascularization

Experimental and Clinical Critique

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Introduction

The greatest killer of the adult [illegible]n male is coronary artery heart disea[illegible]de-generative process associated with [illegible]hero-sclerosis, a disease of aberrant metabolism of fat. Surely, the solution of the problem of atherosclerosis and with it of coronary artery heart disease, as of any degenerative process, must be medical in nature. When enough facts are assembled clinically and experimentally on the subject of the metabolism of cholesterol and other fats and the reasons why they are deposited on the intima of some vessels and not of others, in some people and not in others, in one part of the world more and another part of the world less—and when the presence of these aberrations can be detected clinically and then treated medically—then the treatment of coronary artery heart disease will be exclusively medical in nature. Until that happy day, however, the pursuit of a means to lengthen the life of patients afflicted with coronary artery heart disease, whose lives are ever threatened, is a legitimate pursuit, no less so than the various operative procedures in use clinically today for the saving of a limb or the conservation of tissue by performing an amputation as distally as possible.

In that pursuit we have directed our attention toward the various procedures, historical and current, designed toward the revascularization of the myocardium. In addition we present a brief critique of our experimental and clinical observations to date.

Although it is true that atherosclerosis of the arteries of the heart may proceed gradually and at a relatively slow rate, similar to those of other organs, sudden occlusions of one of the major vessels of the myocardium, which occur all too commonly, present a unique problem in management of the entire patient. This, because the heart has no substitute or replacement for practical purposes. The heart is a single organ. It is not one unit among many, as are the paired kidneys, each of which consists of about 2,000,000 independent functioning units. The heart must do its work without help from any other pump. Occlusion of a major coronary artery may produce death in one of two main ways: 1. Death or necrosis of muscle (myocardial infarction) or its sequelae: The more muscle that is necrotic (and it is the left ventricle which is involved), the less efficient will the heart be and the more commonly will it fail as a pump-unit, and heart failure ensue. Sequelae of the muscle death include rupture of the myocardial wall and thromboembolic phenomena consequent upon mural thrombosis. 2. Rhythm death: Occlusion of a very small branch of a coronary artery or of numerous such branches may cause death without there actually being muscle necrosis or infarction. The pathogenesis of this death is the creation of a temporary ischemic area in the muscle, which becomes an irritable focus and produces dysrhythmia of the heart. If this dysrhythmia should take the form of

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ventricular fibrillation, the patient may die rather suddenly and autopsy reveal no heart muscle death.

Protection of an ischemic area of myocardium against both a rhythm death and muscle death may be provided either by bringing a new source of blood to the myocardium (extracoronary circulation) or by redistributing the blood that is brought to the coronary vessels from the aorta (intercoronary anastomoses). Beck and his associates, in Cleveland,* have attempted to revascularize the myocardium by both of these methods since 1935; Gross, Blum, and Silverman[5] in 1937 first suggested the increase in blood supply to the heart muscle by means of ligation of the coronary sinus. This was also attempted at about the same time by Fauteux.[8] The Cleveland group has also performed cardiopericardiopexy during the past 20 years with numerous substances, of which the best seems to be granulated asbestos powder. Others have adopted this technique using other substances.

Beck and his group have used a standard means of comparison for any possible improvement conferred upon the dog heart by either of the operations which they have performed. The standard test model has been a dog's heart in which a major branch of the coronary system was ligated at its origin; either the descending branch of the left coronary artery or the circumflex branch was used. Ligation of such a vessel at its origin, in their laboratory, produced a mortality of 70%, and this within an average of 13 minutes. The efficacy of a revascularizing procedure was tested by subjecting it to the same ligation subsequently. They have reported a reduction in the early mortality to 10% by arterialization of the coronary sinus and to 30% by ligation of the coronary sinus and cardiopericardiopexy. They have also exhibited injection-corrosion specimens showing an increase in the number of intercoronary channels, i. e., in anastomoses between the branches of the existing three major coronary arteries after a revascularization procedure. Eckstein, Leighninger, and associates,[6] using the technique of Mautz and Gregg,[7] have presented some evidence that the intercoronary channels are functioning by demonstrating an increased flow from the distal end of the cut circumflex artery after a revascularization procedure. It was their interpretation that a few cubic centimeters of blood per minute so contributed was the method that afforded protection to the myocardium after the test ligation of a major coronary branch.

We were impressed with the apparent improvement that had been experienced by human patients who had undergone the revascularization procedures at the Western Reserve University. We were impressed with their ability to return to gainful employment and, most of all, with their freedom from—or reduction in—pain. It appeared to us that there was sufficient evidence in the statistics, both clinical and experimental, from the Beck laboratory to indicate that the arterialization of the coronary-sinus procedure is not indicated. It appears that the workers who first introduced this operation now agree with this opinion.† However, the operation of ligation of the coronary sinus combined with cardiopericardiopexy (with granulated asbestos) offers a procedure which has a low mortality (5%), and offers good and excellent results in just as high a percentage of cases.‡ It became our intent to investigate the modus operandi of benefit from this procedure and to pursue the problem further both experimentally and clinically.

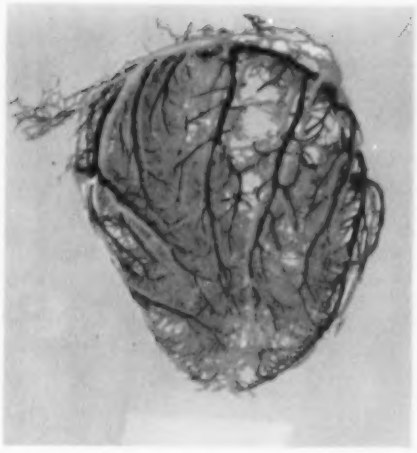
Methods

Mongrel dogs weighing from 10 to 25 kg. were used. Anesthesia was induced with thiopental (Pentothal) sodium intravenously; the animal was then intubated with an endotracheal tube, and the latter attached to a regulation anesthesia machine for the continuation of the procedure under ether and oxygen. The cuff on the endotracheal tube was inflated immediately before opening the pleura. Aseptic operating room technique was used

* References 1-4.

† References 3 and 4.

‡ References 3 and 4.



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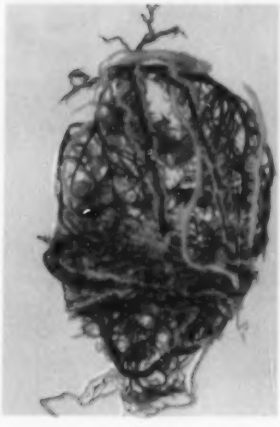

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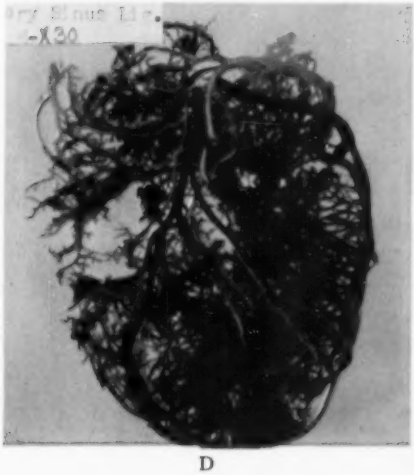

D

E

Figure 1

Injection-corrosion specimens. Coronary arteries in red; coronary veins in yellow; embedded in plastic. A, normal; B, and *B Apex*, normal — note heavy anastomoses at apex of heart; C, multiple twig ligations in apical one-third of heart — note anastomoses in this area; D, coronary sinus ligation; E, coronary sinus ligation. Note lush arterial vasculature and meager venous vasculature in D and E.

throughout. The animals received penicillin intramuscularly after the operation and on one or two postoperative days. Electrodes were attached to all four limbs and connected to the direct-writing electrocardiograph.

In 10 animals multiple secondary branches of the coronary arterial tree (twigs) were ligated with cotton sutures. In 13 animals the origin of the descending branch of the left coronary artery was dissected with fine instruments to show the bifurcation between the descending and the circumflex branches, and then the descending branch was ligated in this crotch.

In 22 animals the coronary sinus was ligated with a nonabsorbable (cotton) surgical suture 5 to 10 mm. proximal to its entrance into the right auricle.

In every instance the chest was closed without drainage after the lungs had been expanded with positive pressure.

All injection-corrosion specimens were prepared in the following manner: After removal of the heart the right and left coronary arteries were injected through their ostia in the aorta with red vinyl plastic; the venous system of the heart was injected through the coronary sinus with yellow vinyl plastic. The hearts were then corroded in a sodium hydroxide bath until only the vinyl plastic material remained as a cast of the vascular tree. The cast was then embedded in plastic material.

Experimental Results

Using a modified Schlesinger injection-corrosion technique as described above, we found the arterial vasculature of the normal dog heart to be somewhat more lush than reported in the literature by others. One-half of all the normal dog hearts thus prepared show excellent anastomoses between the three existing main coronary artery channels (Figs. 1*A* and 1*B*). Indeed, some of our normals appear to have as lush an arterial vasculature as the "after-operation" specimens published by others.

Twig Ligations

It has been reported that multiple ligations of small twigs near the apex producing a blue, cyanotic, ischemic area may act as a trigger mechanism and produce ventricular fibrillation and thus a rhythm death. We have ligated not only four or five twigs in an area but as many as eight, producing an area of ventricular myocardium as cyanotic as indigo. The mortality rate, however, was found to be only 20%, and this 20% did not die within an hour but, rather, between 24 and 72 hours after the operation (Table 1).

TABLE 1.—*Multiple Twig Ligations*

Dog	Procedure with Early Result	Late Result
1	5 twigs ligated Deep-blue area at apex	Killed 15 mo. later
2	5 twigs ligated Deep-blue area at apex	Killed 13 mo. later
3	5 twigs ligated Severe color change of ½ of anterior wall	Killed in epinephrine sensitivity test 8 mo. later
4	5 twigs ligated Deep-blue area at apex	Died on 3d day
5	7 twigs ligated Deep-blue apex	Killed 16 mo. later
6	8 twigs ligated Very lush connections of all vessels noted preoperatively	Last to study after 12 mo.
7	5 twigs ligated Blue apex	Multiple ligations repeated 10 mo. later
8	5 twigs ligated Blue anterior wall	Last to study 1 mo. later
9	6 twigs ligated Marked blue anterior line	Killed 15 mo. later
10	4 branches of left descending, 1 branch of circumflex, and 1 branch of right coronary arteries ligated	Died on 3d day

Test Model Ligation

We felt it would be desirable to have our own controls on the mortality rate of ligation of either the descending branch of the left coronary artery or the circumflex artery at its origin. Accordingly, we isolated, by gentle dissection, and ligated the descending branch of the left coronary artery at its very origin (Fig. 2) with electrocardiographic tracings before, during, and after the procedure. We were surprised to find only a 23% mortality rate following this procedure (Table 2). This was the case despite the fact that the electrocardiographic tracings showed marked changes (Fig. 3) and a discolored cyanotic area on the ventricular myocardium, startling in degree, was produced from the base to the apex. These animals were autopsied; a marked adhesive pericarditis was found in the 80% of animals that lived. In the animals that died following this procedure it was found that the septal branch had also been ligated, together with the descending branch of the left coronary artery (Fig. 2, *a* and *b*).

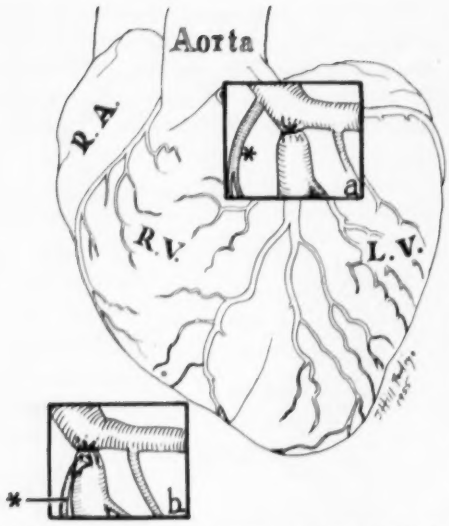

Fig. 2.—Ligation of descending branch of left coronary artery at its origin. Insert *a* shows origin of septal branch (*) proximal to bifurcation of left branch. Insert *b* shows origin of septal branch distal to ligature in crotch of bifurcation.

Coronary Sinus Ligation

Early in the progress of this work animals that were autopsied three to five weeks after complete ligation of the coronary sinus were found to have a diminution in the number of venous channels in the myocardium and a more lush arterial vasculature (Fig. 1*D* and *E*). This was not true in all specimens but was true in somewhat more than half of such specimens. Animals autopsied in from 6 to 12 months after ligation of the coronary sinus did not exhibit this lush myocardial arterial tree.

Upon reflection it is really not surprising that newly created vasculature is not sustained in the normal dog heart. In 1909, Halstead enunciated the principle that changes can be created in living organisms when there is a need or demand for the change to the new status. This principle applies most particularly to the homologous transplantation of tissue but also is applicable to the revascularization of an organ. As implied, there must be a deficient vascularization to require a new vasculature. The test model for revascularization will therefore be an animal with a chronically inadequate coronary blood supply. We are engaged at the present time in producing chronic coronary insufficiency in the dog by the method of Monroe, Balchum, Owens, and Swan [9] in order more critically to evaluate this method of revascularization. With such preparations we are now engaged in testing both the coronary sinus ligation technique and the Vineberg operation.

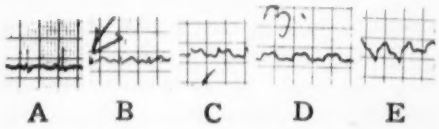

Fig. 3.—Ligation of descending branch of left coronary artery. *A*, control at 2:51 p.m.; *B*, ligation at 2:53 p.m.; *C*, 2:55 p.m.; *D*, 303 p.m.; *E*, 3:22 p.m. Complete recovery ensued.

Clinical Results

Clinically we have adhered to the indications and contraindications as laid down by Beck and his group from their experience. The main indications for the use of the myocardial revascularization procedures are (1) a relatively young man who has had one or more proved myocardial infarctions, (2) continued disabling pain following an infarction, usually with electrocardiographic evidence of chronic insufficiency, and (3) status anginosus. The contraindications are (1) a heart in failure, (2) a grossly dilated

TABLE 2.—*Ligation of Anterior Descending Branch Left Coronary Artery*

Dog	Result	Remarks
19	Lived	
21	Lived	
35	Lived	
36	Lived	
37	Lived	
38	Died within 24 hr.	Septal branch ligated with descending Several minutes of asphyxia during operation; previous coronary sinus ligation
39 (12)	Lived	Previous coronary sinus ligation
40	Lived	
41		Died when circumflex also ligated; septal branch ligated also
42	Lived	
43	Lived	
44	Lived	
11	Died within 24 hr.	Septal branch ligated with descending

heart, and (3) less than six months following a proved myocardial infarction. Adherence to the contraindications is important, because a heart which is failing as a unit-pump cannot be revascularized, since too much of its muscle has been replaced with scar tissue; it is in this group of patients that one would experience a high mortality, for they cannot withstand the operative procedure.

The improvement conferred upon properly selected patients cannot seriously be doubted. One of us (E. M.) has performed the operation of coronary sinus ligation with cardiopericardiopexy in five cases. There has been no operative or early postoperative mortality. The only late mortality was exactly one year after the operation and occurred in the one case in which the limits of indications were exceeded, in that the patient had been in failure shortly before the operation and was 62 years of age. During the year that he lived postoperatively he was ambulatory and not in congestive failure for 10 of the 12 months. The only mortalities were those that occurred 4, 7, and 14 days, respectively, before the patient's scheduled day of operation. Abstracts of the clinical cases follow.

CASE 1 (courtesy Dr. Sylvan Solarz, Michael Reese Hospital).—A 45-year-old white man, machine operator, with history of three hospital admissions for severe and prolonged anginal pain with ECG changes over 13 months' time (July, 1952 to August, 1953). Status anginosus from August, 1953, to time of operation, with use of glyceryl trinitrate U. S. P. sublingually several times daily. Total period of complete disability, 19 months. Coronary sinus ligation and asbestos cardiopericardiopexy on Feb. 1, 1954. Marked diminution in angina by the 12th postoperative week. Has worked since four months after operation. Feels need of a glyceryl trinitrate tablet sublingually only once every three to five months.

CASE 2 (courtesy Dr. A. L. Hickman Jr., St. Margaret Hospital, Hammond, Ind.).—A 41-year-old white man, railroad office worker, with history of 19 months of status anginosus, during which time he had two proved myocardial infarctions. He used 1 to 12 tablets of glyceryl trinitrate daily during most of this period. Numerous episodes of his angina were monitored by ECG tracings, which showed marked ischemic changes. Several episodes of angina occurred at the ages of 35, 36, and 37. One brother had an arteriosclerotic occlusion of a popliteal artery at the age of 51; their mother died of coronary disease. Coronary ligation and asbestos cardiopericardiopexy on Feb. 2, 1954. Has taken no glyceryl trinitrate since 12 weeks postoperatively, has worked since four months postoperatively, plays golf once a week.

CASE 3.—A 45-year-old white man, electric welder, who had a proved myocardial infarction with congestive heart failure in 1952, at the age of 42, and who has had angina since 1953, especially on exertion and after meals, but also at rest and at night. Angina relieved with rest and by narcotics. Increased frequency of anginal episodes during first six months of 1955. Coronary sinus ligation with asbestos cardiopericardiopexy on Aug. 1, 1955. Continued to require glyceryl trinitrate for first three postoperative weeks. Thereafter patient used no glyceryl trinitrate except for 48-hour period in last week of December, 1955, when he was passing a calculus down the right ureter. Returned to work in 12th postoperative week. Continues to have occasional angina only on exertion, relieved by glyceryl trinitrate.

CASE 4.—A 53-year-old white man, milkman, who had had four prolonged periods over a three-year span of burning substernal pain with a sensation of "someone sitting on my chest." These episodes were precipitated by walking and by climbing stairs, and were relieved by the use of glyceryl trinitrate. Moderate hypertension of 170/100 was very constant. Coronary sinus ligation and abestos cardiopericardiopexy on Sept. 29, 1955. No angina experienced for three months postoperatively. Mild angina in early January, 1956, consequent upon excitement over an insurance examination and refusal of his employer to reassign him to a less strenuous job.

CASE 5.—A 62-year old white man, carpenter, with progressive dyspnea of two years' duration, ECG evidence of chronic coronary insufficiency and of a myocardial infarction on June 7, 1953. He rebelled severely against a rocking-chair existence. Exploration on Oct. 15, 1953, revealed a myocardium so sensitive that it could not tolerate constriction of the coronary sinus. Accordingly, this was abandoned and an asbestos cardiopericardiopexy was done. Patient's condition was precarious for three days (congestive heart failure and dysrhythmia with fast rate). Thereafter he improved rapidly and became compensated and ambulatory. From the third postoperative month he walked around the yard, did a little carpentering, and experienced no dyspnea or pain. In the 11th postoperative month he developed mildly congestive heart failure, and one year to the day after the operation he died suddenly, while riding in a car.

Comment

Ideally the etiology and pathogenesis of a disease should be understood in order that its effective treatment may be rational, direct, and definitive. In much of medicine today this does not obtain; empiricism exists because of lack of knowledge; treatment is employed which confers benefit even if the method of benefit is not understood. Would that all we see in medicine could be understood and that all of the treatment that we proffer to our patients would be direct and definitive. That would be ideal. But we must be practical, and extend to our patients the help that we can whether unequivocal experimental evidence for it exists or not. To doubt that much benefit is gained from the revascularization procedures mentioned is to bury one's head in the sand. With the work now going on in many laboratories throughout the world probing into the secrets of fat metabolism and atherosclerosis, we can look forward to treating the ravages of atherosclerosis in the human being by logical and rational means. This is for the future. Today we must attempt to revascularize the myocardium, in any suitable manner, if there exists clinical evidence that improvement is conferred by these procedures. The promise of the future does not negate the armamentarium of the present.

In treating malignancy we have accepted operative procedures which are not curative, but only palliative, in that the patient may live longer but still have the malignancy. This should be no less true in cardiovascular disease if longevity can be conferred in some degree although the degenerative disease is not cured. If an operation can increase longevity, it is a worth-while operation even if the experimental reason for the operation is not adequately at hand. To the patient with the disease the operation is desirable even if its methods of producing improvement are not understood.

It is our opinion that the operation of ligation of the coronary sinus and asbestos cardiopericardiopexy is warranted in properly selected cases. It is further our opinion that evidence that this procedure does revascularize the myocardium is not as easily obtainable or available in the normal dog heart as the more enthusiastic would have us believe. This is really not difficult to understand for the simple reason that the normal dog heart does not need revascularization. It is more logical to expect the heart which is in need of revascularization to develop new channels in distribution than the normal heart, which has no insufficiency of blood supply (see above). Until recently there has been no completely satisfactory means of simulating, in the experimental normal dog heart, chronic coronary insufficiency as it occurs in man. However, with the recent method suggested by the Denver group [9] we hope to be able to supply requisite information.

Summary and Conclusions

1. Coronary artery heart disease is a degenerative disease and is the number one killer of the adult male.

2. Atherosclerosis, the basic pathology of coronary artery heart disease, is an as yet incompletely understood aberration of fat metabolism. The understanding of the pathogenesis of atherosclerosis and its prevention will ultimately be the definitive treatment of coronary artery heart disease.

3. The mortality rate of ligation of the descending branch of the L. coronary artery in 23% in our laboratory. Death occurred only when the septal blood supply is also cut off.

4. Revascularization of the myocardium can protect the heart in properly selected cases from death in subsequent coronary occlusions. It can prevent pain of ischemia by redistributing blood more uniformly throughout the myocardium.

5. We hope to demonstrate the method of this improvement using a new preparation in which chronic coronary insufficiency is created in the dog heart.

Drs. Louis N. Katz and Jeremiah Stamler gave guidance and advice, and Mr. Charles Jones prepared the injection-corrosion specimens.

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Spontaneous Hemopneumothorax

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By definition, spontaneous hemopneumothorax is the sudden entrance of air from the lung into the pleural space with concomitant bleeding into the pleural space in the absence of external precipitating factors. The qualifying adjective "nontuberculous" is sometimes added as a prefix to designate this disease.

History

In 1900 the first reports of this disease were made by Pitt,[12] Rolleston,[14] and Boland,[2] independently of each other. Hartzell,[9] in 1942, collected from the literature 40 instances of this disease and added 3 more case reports. By 1950 ninety-three cases were on record and certainly the diagnosis was being made with increasing frequency. The mortality rate among the reported cases was 20%, and this included mild as well as severe degrees of involvement.

The development of thoracic surgery and the elucidation of principles of treatment of chest injuries with traumatic hemothorax laid the background for the surgical treatment of this condition. Elrod and Murphy,[6] in 1948, reported the first thoracotomy performed for decortication of spontaneous hemopneumothorax residuals. Seley and Neuhof,[17] in 1951, reported a similar case history, of a patient whom they had treated in 1936. It was Myers,[11] in 1951, who demonstrated the fact that surgery is the treatment of choice during the acute phase if the bleeding and the disturbed pulmonary physiology endanger the life of the afflicted. Beatty and Frelick[1] reported results in treatment of three patients during the acute phase by controlling the hemorrhage, restoration of normal intrapleural pressure, and expansion of the lung. A number of subsequent reports have made their appearance, and this is the 17th reported case.[1,3,4,7-11,15,16,19] There have been no deaths among the patients treated in this manner.

Etiology

Autopsy and surgical findings have incriminated apical cysts or blebs with associated vascular adhesions as the immediate source of the air and the blood. The age incidence of this disease and its absence in the age group in which degenerative lung changes are most commonly found give cause for speculation as to the true etiology. The infrequency of this condition in females may provide a clue as to causative factors.

Pathology

The rupture of a bleb results in a partial collapse of the involved lung as the negative intrapleural pressure is replaced by a positive pressure. As the lung collapses traction is exerted on existing pleural adhesions; laceration may result and hemorrhage may occur. If the bleeding is from the systemic circulation (via the intercostals or internal mammary vessels), in contrast to pulmonary circulation (bleeding from the lung itself), the blood loss is thought to be much more significant because of the greater hydrostatic pressure in the systemic circulation. The rupture of a bleb is not necessarily related to physical activity in any consistent cause and effect relationship.

The accumulated blood, for the most part, becomes defibrinated by the rhythmic motions of the diaphragm, heart, thoracic wall, and lung. The fibrin is deposited on the pleural

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surfaces adjacent to these structures. Small clots are usually found intermingled with this resultant defibrinated "blood." The fact that this "blood" would not clot on aspiration caused considerable confusion in years past and probably contributed to the delay in recognition of the true pathologic changes taking place within the pleural space. If bleeding is massive, the aspirated blood may be found to clot because it has not had sufficient time to become defibrinated. This observation should cause the clinician alarm in view of the alacrity of the bleeding.

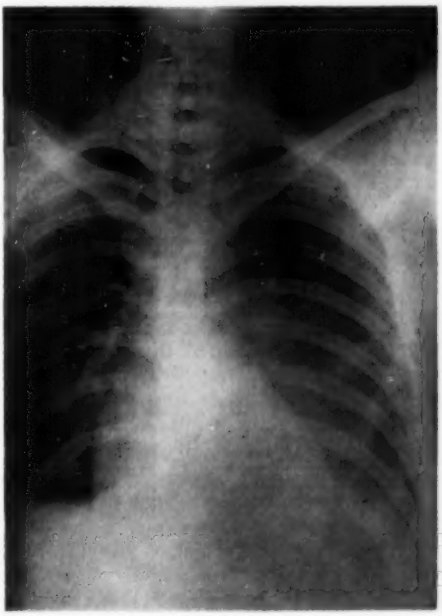
The deposition of the fibrin has a twofold harmful effect on the patient's pulmonary capacity. In the first consideration, it occupies space that belongs rightfully to pulmonary tissue engaged in gaseous exchange. Secondly, and more seriously, the fibrin organizes to a dense scar tissue. This dense scar tissue can convert the chest wall, with its normal bellows action, into an immobile, unexpansive chest cage. In a similar fashion, the action of the diaphragm becomes severely restricted because it is tenaciously adherent to the chest wall and covered with a thick layer of unyielding scar tissue, preventing its inherent piston-type of action. The function of the entrapped lung is limited by the lack of gaseous exchange within its bronchioles and alveoli—the lung cannot expand and deflate.

Clinical Features

Symptoms.—The rapidity and extent of the penumothorax accumulation, the amount of mediastinal shift, and the amount and rapidity of blood loss will ultimately determine the severity of symptoms and findings. At the onset the symptoms typically appear with a suddenness and a severity that may seem catastrophic. The onset may be gradual, even being insidious. The cardinal symptoms are chest pain, dyspnea, weakness, apprehension, and faintness. Occasionally the pain has been referred entirely to the abdomen, mimicing perforated viscus. Shoulder pain is not uncommon; syncope may occur. Coronary vascular disease is strongly suggested by the symptoms in certain cases. The sudden onset may be followed by a period of remission, with a subsequent recrudescence of complaints as the intrapleural air and blood increase in amount.

Findings.—In the acute phase the findings of shock, with a rapid, thready pulse, pallor, apprehensive or anxious facies, moist skin, and a low blood pressure, are present. The primary shock noted at the onset may later be replaced by secondary shock following blood loss and/or mediastinal shift with incomplete filling of the right heart. The dyspnea and pain may be associated with restlessness and cyanosis. Breath sounds are distant or absent on the involved side, often in a spotty fashion. In like manner, percussion of the chest may be tympanitic, especially early in the course of the disease. Later dullness becomes evident as fibrin and blood accumulate. The following case history is typical of this disease.

Fig. 1.—Chest x-ray the day of onset of symptoms.



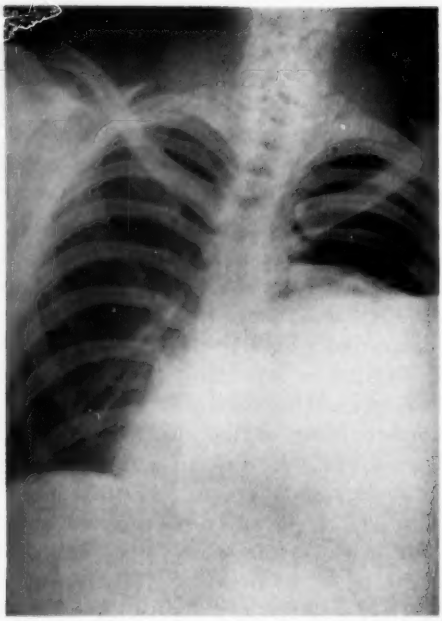


Fig. 2.—Chest x-ray the day after onset of symptoms; symptoms unchanged.

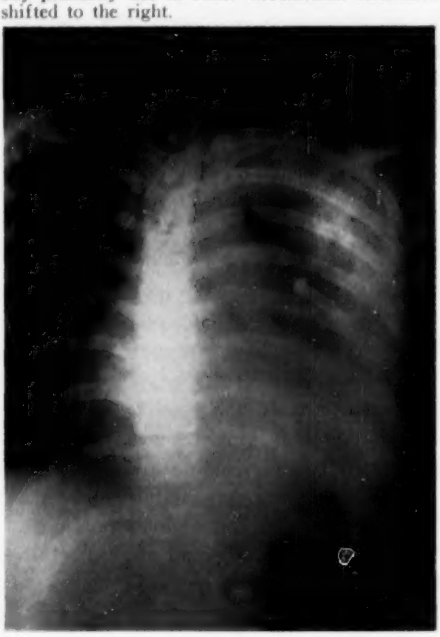
Report of a Case

A 24-year-old white man experienced sudden persistent pain in the left chest while sitting at his desk. This was aggravated by deep respiration and was associated with a "catch" in his chest. He stated that he had had a "cold" with a mild cough during the preceding two weeks and had noted momentary pain twinges in the left chest on several occasions. The only physical findings of significance were diminished breath sounds over the left chest in an apprehensive patient who was cold, clammy, and pale. An electrocardiogram was normal. On April 22, 1955, the following day, a chest x-ray (Fig. 1) revealed a 25% collapse of the lower lobe. Red blood cell count was 5,700,000 cells, and the white cell count was 15,000 per cubic millimeter.

The above complaints persisted. The following day his pulse rate was reported as "rapid" and his complaints continued. An x-ray of his chest now revealed a fluid level, with greater collapse of the lung (Fig. 2). On thoracentesis 500 cc. of bloody fluid was aspirated. A chest tube was inserted, and a mixture of air and bloody fluid was obtained in an unrecorded amount. Underwater seal drainage was continuous, and improvement in the condition of the patient resulted. The red blood cell count was 3,650,000, and the white blood cell count was 27,000 per cubic millimeter; hemoglobin level was 10.5 gm. A transfusion of 1500 cc. of whole blood was administered.

Left chest pain was persistent and associated with dyspnea. No record of the amount of pleural drainage during these days of hospitalization was obtained. Bleeding was active, as evidenced by the drop in blood cell count despite transfusions—the hemoglobin level dropped to 9.3 gm.; the red blood cell count was 3,280,000 per cubic millimeter, and the white cell count was now 10,000 per cubic millimeter of blood. He was admitted to our hospital via ambulance late in the evening of the fourth day. He appeared tired, apprehensive, and dyspneic despite continuous oxygen administration. Chest pain was his chief complaint. On examination his blood pressure was 115/82 mm. of mercury, with a pulse rate of 128 per minute; his respirations were shallow and guarded, with a rate of 32 per minute. Oral temperature was 102.6 F; the trachea was slightly to the right of midline, and breath sounds were absent over the left chest. The intercostal tube did not appear to be functioning, and so a thoracentesis of 1000 cc. of bloody fluid was performed. In addition, the patient was given a transfusion of 500 cc. of whole blood. Prior to this, the hematocrit level was 33%, bleeding and coagulation times were normal; hemoglobin level was 11.5 gm. after the transfusion. Chest film taken at this time dis-

Fig. 3.—Appearance despite adequate pleural drainage with thoracotomy tubes. Increased density primarily due to clots. Mediastinal structures shifted to the right.



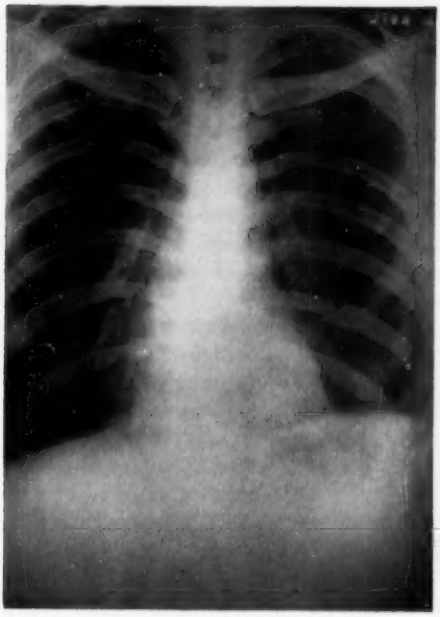


Fig. 4.—Follow-up film three weeks postoperatively.

played generalized patchy type of opacification involving the left thorax, with very little visualized lung aerated. This condition persisted until the time of surgery (Fig. 3). Breath sounds were faint and distant anteriorly over the left chest after thoracentesis.

The following morning the patient was transferred to the surgical service, and it was noted that there was no drainage or tidaling in the thoracotomy tube or in the more recently inserted Clagett needle. He was taken to the operating room for irrigation of the thoracotomy tube; if active bleeding was observed, thoracotomy was to be undertaken. Upon inserting a new tube intercostally and removing the previous one, irrigation resulted in the removal of 750 cc. of bloody fluid in excess of the irrigating fluid. The fluid obtained was not fresh blood. The trachea was again in the midline and there was improvement in the dyspnea, and so no further measures were undertaken. Nevertheless, the chest roentgenograms taken immediately after this showed no improvement (Fig. 3). A septic type of temperature curve, with peaks of 103.6 F orally, was recorded. His condition remained serious; an additional intercostal tube was inserted, since the one in situ appeared to function intermittently. Streptokinase-streptodornase (Varidase), 250,000 units, was instilled into the left chest in an attempt to liquefy the fibrin and clot. No benefit was noted (this agrees with the experience of others[9,18,38]).

On April 29 an open thoracotomy, evacuations of blood clots, and decortication of early fibrin deposits were accomplished. Because of the dense coating of fibrin and enmeshed red cells it was not possible to locate the area of previous bleeding and air leakage. There was no evidence of active bleeding except for pinpoint bleeding from the pericardium when the fibrin was removed. It appeared to be more tenaciously adherent here, with greater organization than elsewhere. There were several small apical postinflammatory blebs, the largest of which was less than 1.0 cm. in size. The clots were few and for the most part very small. Fibrin, much of it shaggy in appearance, formed the bulk of the organizing mass.

Convalescence was uneventful. The patient returned to work two weeks postoperatively. Smear and culture for acid-fast organisms were negative, and no evidence of pyogenic organisms was found. The pathologist's report was "fibrin, organizing blood clot with no evidence of malignancy, or specific inflammatory organisms."

Treatment

The treatment of hemopneumothorax was formerly associated with a high mortality rate, as shown in Hartzell's series (32%). Our efforts to select the best mode of therapy must encompass not only a mortality reduction but also a reduction in morbidity. A review of case histories of the survivors in the early presurgical era demonstrates the prolonged convalescence that these patients underwent. The desired end-result is a complete and early reexpansion of the lung. In this manner we can obviate much suffering, and the patient can return to his family and occupation at an early date.

The basic principles of treatment do not seem to differ significantly from those employed in treating hemopneumothorax of traumatic origin. In essence, the disturbed physiology centers about two factors:

1. Cardiorespiratory embarrassment due to accumulation of blood and air in the pleural space. There results a loss of pulmonary reserve, incomplete filling of the right heart due to mediastinal compression and vascular angulation, and, because of these changes or separate from them, the undesirable effects attributed to vagovagal reflexes.

2. Blood loss with resultant anemia and inadequate circulating blood volume. This can progress to shock, visceral anoxia, and/or exsanguination.

These two factors coexist in varying degrees of severity, and their effects on the patient are additive. The pneumothorax usually preceeds the bleeding.

Thoracentesis is the first step in treatment and is employed also as a diagnostic measure concomitantly. The identification of the fluid as blood is made possible at the time of thoracentesis; during the procedure all of the air and the blood should be aspirated from the pleural space. Many still hold with the concept of maintaining an uncertain degree of lung collapse, some even expressing this as a "tamponade" effect on the fistulous opening as well as the bleeding point. Complete pulmonary expansion should be promptly achieved, and reaccumulation may not occur, or it may be so slight that it can be controlled by repeat thoracentesis.

Closed thoracotomy and catheter drainage is a more satisfactory method. It is generally the minimal requirement in treating massive hemopneumothorax, but even it will rarely permit egress of all clots. The use of streptokinase-streptodornase has been recommended in this regard, and it should be used intrapleurally only with ready access to pleural drainage such as is afforded by a tube. These closed methods of treatment have handled the "pneumo" portion of this disease very well. In the presence of massive bleeding, the above-described methods have proved inadequate. The patient may exsanguinate from uncontrolled bleeding, or recovery from the bleeding episode may be followed by pulmonary invalidism as a result of a lung trapped in organized fibrin and blood clot.

Repeated and close observation of these patients is necessary to determine the rapidity of blood loss. The prostration often associated with sudden onset of symptoms is not due to blood loss and is self-limiting. Should it persist, or recur, there is cause for alarm. Serial roentgenograms of the chest, measurement of pleural drainage, and repeated blood counts are necessary, as is close observation of the pulse and respiratory rates and blood pressure levels. In cases of minimal bleeding repeat chest roentgenograms should include oblique positions to determine more accurately the amount of fluid and fibrin deposition in the costophrenic sinuses. Blood volume studies may be of help.

Thoracotomy is indicated immediately if (*a*) intercostal tube drainage is inadequate in removing intrapleural blood or air and the accumulation is progressive owing to continued bleeding or air leakage; operation should not be deferred as an eleventh-hour procedure; (*b*) blood loss is so rapid that transfusion replacement is necessary to prevent shock.

Delayed thoracotomy is undertaken for (*a*) continued bleeding at a slower rate than described above (the patient suffers no cardiorespiratory difficulties, but bleeding continues as shown by the examinations mentioned above, and transfusions are indicated); (*b*) accumulation of intrapleural clots of fibrin and/or blood, despite more conservative methods of evacuation; (*c*) fibrothorax. This is the late effect of the disease and ideally should be prevented by application of the foregoing measures. Decortication of the organized fibrous peel improves pulmonary function.

Summary

The air leak is readily controllable in hemopneumothorax.

In cases of minimal bleeding repeat chest roentgenograms should include oblique positions to determine more accurately the amount of fluid and fibrin deposition in the costophrenic sinuses.

The blood loss is variable, and surgical judgment dictates the necessity of definitive treatment, as is required for hemorrhage in other areas of the body.

Adequate intercostal tube drainage is a more reliable, quicker and more thorough

method of removing air and blood from the pleural cavity than is thoracentesis.

If fibrin and blood clot render tube drainage inadequate, or continued bleeding endangers the patient's welfare, open thoractomy is necessary to insure recovery.

Seventeen seriously ill patients (cases collected from the literature and the one reported on here) have been treated by open thoracotomy as a life-saving measure and/or to prevent prolonged debility and pulmonary invalidism. There has been no mortality, and rehabilitation has been prompt and complete.

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The Homograft Rejection Mechanism

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Introduction

The general purpose of this study was to learn more about the homograft rejection mechanism. We realized that previous studies were not clear as to the morphology and dynamics of grafting. Only by animal study can the variables be sufficiently controlled to draw reliable conclusions.

We selected a small mammal because of known similarities to the human, in giving birth to living young and in the existence of species individuality.

The mouse seemed ideal, since the development of inbred strains has given us individuals that are so nearly identical, genetically, that tissues may be transferred between individual isogenic mice with the same success encountered when autografting in the human. Recently, Eichwald [8] has shown that certain isogenetic grafts from males onto females will not "take" as consistently as autografts, but in general these strains are comparable in genetic similarity to human identical twins. Thus the isograft in the mouse seems to obey all of the laws of autografting in the human. Conversely, if grafts are transferred, as homografts, between two different inbred strains such as the CBA black and the A-line white, the grafts fail with the same consistency and completeness that homografts do in the human.

Sandison in 1924 [1] and Clark in 1930 [2] developed the use of a transparent chamber that could be used on the ear of the rabbit. This intriguing idea was aimed at an attempt to permit high-power microscopic observations in vivo. These early chambers were rather heavy and cumbersome, and the visibility left something to be desired.

It remained for Algire and his colleagues to modify and adapt the principle of the transparent chamber to the mouse by using a dorsal fold of skin. His beautiful studies over the past decade have been milestones in the field of experimental physiology.[3] In 1952 we had the occasion to visit Dr. Algire and watch him demonstrate his meticulous transparent chamber technique. It seemed obvious that this tool offered a chance to study many of the vascular reactions in grafting. Our own attempts to set up similar chambers in the laboratory soon made us appreciate that the problems of sepsis and mechanical failure could lead to confusion in the interpretation of many results.

Particularly in the case of skin grafting, we found that there was ever need for a lighter and more physiological type of splint. Accordingly, there has been a constant evolution in the design of our splints and chambers, with emphasis on reducing weight and traumatic irritation to a minimum. The use of a light copper wire frame, as suggested by Joslin,[4] was a most helpful addition. The resultant splint differs in several important particulars from its predecessors [5] (Figs. 1 and 2).

With our earlier chambers we found that grafts of skin were so dense that really clear observations of vascular changes were essentially limited to the periphery of the grafts. Good refraction demands good light transmission through the graft and its bed. Thus, observations became more accurate when we learned that we could place the skin graft, without glass or lucite covering,

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From the Division of Plastic Surgery, The Johns Hopkins Hospital and The Johns Hopkins University School of Medicine.

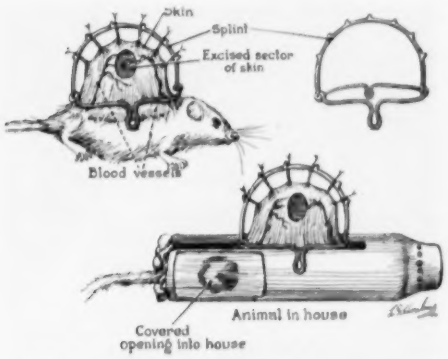

Fig. 1.—A fold of dorsal skin is held up by means of a half-circle splint of copper wire. Tantalum or Stainless Steel sutures are used to secure the skin fold to the splint. The two side arms or "outriggers" stabilize the splint in vertical position. At the bottom the mouse is shown in the brass holder used for microscopic viewing. A strip of cellophane (Scotch) tape covers an opening in the cylinder through which a leg may be drawn for various injections.

on a recipient bed dissected for that purpose, on one side of the dorsal fold. The corresponding skin surface on the opposite side of the dorsal fold can then be cut away and a round glass cover slip inserted to give visual access to the deep surface of the graft (Fig. 2). The external surface of the skin graft is thus exposed to the air in a physiological manner, and normal skin changes such as keratinization and epithelial shedding can take place and be observed. This circumvents the artificial environment necessary in previous transparent chamber studies of skin grafts, when these grafts were enclosed under a glass or plastic covering. It also permitted a direct view of the host vessels immediately beneath the graft, and revealed vascular activity that had been hitherto unsuspected. These newer splints have permitted graft observations for as long as 65 days, consecutively. This period can be extended indefinitely by "delayed" application of the chambers.

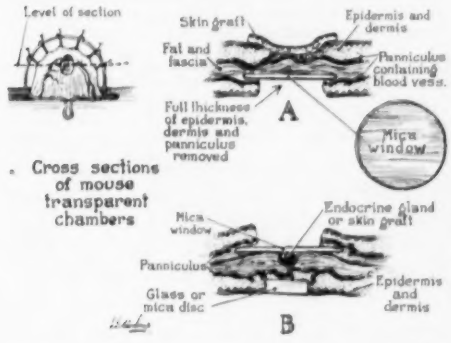

Fig. 2.—At the upper left, the dotted line represents the level of cross sections shown in *A* and *B*. *A* shows the recent physiological type of chamber that may be used to study skin grafts. Note that, except for the graft itself, light need be transmitted only through one layer of fascia and one layer of blood vessels. The mica or glass window is held in place simply by overlapping skin edges. In this way the trauma from sutures is avoided. In *B* the details are shown of the type of chamber employed in the study of grafts other than skin. The epidermis and dermis have been removed from both surfaces of the skin fold, with great care having been taken to spare the vessels of the panniculus carnosus on the "back" side of the chamber.

Results

Skin Grafting

Many of the experiments now in progress are incomplete, but certain definite conclusions may be drawn.

A few definitions are needed in order to state whether a graft is viable or dead, vascularized or nonvascularized, functioning or nonfunctioning.

Skin grafts are considered to be viable or "alive" when the following observations can be made:

1. The gross texture and pink color of the surface is evident.

2. The pigment and hair follicle pattern of the donor is seen.

3. There is active circulation within blood vessels of the graft itself.

4. These graft vessels show the exact pattern or anatomical relationships of the donor area and not the host bed. The graft vessels should not move with the rhythmical muscle twitch of the panniculus carnosus of the host mouse. The vessel pattern of the graft is usually easy to identify at the time of initial insertion of the graft.

5. Hair growth is seen on the living graft, sometimes within seven to eight days (or earlier with newborn skin).

6. Skin grafts can be "peeled" and, if still vascularized, show active "back bleeding" from the elevated, but still partly attached graft.

7. Microscopic sections taken of the grafts reveal the normal anatomical structures.

8. Removal of the skin graft "ghost" layer and a check of the graft surface under the microscope, using opaque lighting, shows intradermal circulation.

9. The skin graft may be successfully removed and reapplied to the original donor or another isogenic host of the same strain.

Skin Autografts.—Over 300 autografts of skin were studied in both CBA black and A-line white mice. Full thickness grafts from the dorsal surface of the ear and the abdomen were used. These grafts must have meticulous removal of all fat and fascia (as described by Billingham[6]) or gross alterations in the takes and resultant growth rates will be seen.[5]

Several reports have been published that indicate that the vascularization of skin grafts occurs by simple ingrowth of capillary buds from the graft bed. This process may occur, to some extent, but a much more significant role seems to be played by the actual vascular framework of the graft itself.[7] In 54 transparent chambers of skin autografts, we could repeatedly see the actual anastomosis and reestablishment of circulation in the blood vessels transplanted along with the graft. The larger vessels would often first contain the motionless RBC of the donor (Fig. 3). Then, at 48-72 hours after grafting, these vessels appear to dilate slightly and very sluggish movement of the red cells can be seen. Often this takes the form of a to-and-fro rocking movement at first, followed in 24-36 hours by a gradual increase in the speed of the stream, with flow becoming established in one direction. In a few instances

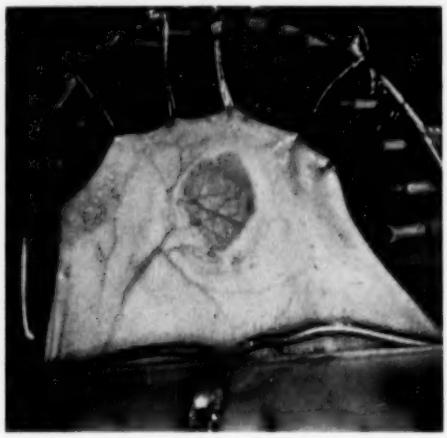

Fig. 3.—A circular full-thickness skin autograft is shown overlying the transparent chamber in an A-line mouse. The skin on the posterior surface of this fold has been replaced by a glass window. The large host vessels can be seen approaching the graft from seven o'clock on the periphery of the graft. The pattern of ear vessels in the graft itself may be seen at nine o'clock on the graft and run across the graft and downward toward four o'clock with several branchings. Under the microscope, on the third day after grafting, these graft vessels have filled with blood and very slow movement has begun. At times this flow may be in the reverse direction of original flow in graft vessels. (Enlargements of later stages are shown in Fig. 4.)

this vascular flow has been observed in the larger graft vessels within 18-20 hours after grafting. Here again we must stress that real variance in the exact time of initial vascularization will be noted, depending upon the size and density of blood vessels in the layer of fascia on which the graft is placed. If the graft is laid on the vascular subcutaneous layer, circulation will appear 48 to 72 hours earlier than when it is placed on the less vascular connective tissue fascia beneath.

Coinciding in time with the true vascularization in the graft, there is a "sympathetic response" in the vessels of the graft bed. This is particularly apparent with a two-sided chamber revealing the deep surface of the graft through the host bed. It consists of a definite dilation and increased flow in the existent bed vessels and an apparent development of many new smaller

vessels that do not appear to have a muscular wall. These latter may, of course, represent mere enlargement of tiny vessels already present. This bed response lasts approximately 72-96 hours. The effect has brought to mind those similar vascular changes seen with reactive hyperemia in the upper extremity of the human, after use of a pneumatic tourniquet. One wonders if the ischemia present in any graft, before it becomes vascularized, does not cause the release of similar metabolites that reflexly bring about this vascular dilitation until the anoxia is corrected.

Even with attention to asepsis some of the chambers will develop an infection. In such instances the vascular changes are quite different and lead quickly to disruption of small vessel endothelium, with extravasation of free red cells and white cells into the tissues beneath and around the graft. This picture is easily distinguished from the pattern of "sympathetic response."

Unlike homografts, autografts show a permanent persistence of their graft vessel pattern for as long as the graft may be identified.

Skin Homografts.—Skin homografts were also studied in a series of over 200 transparent chambers and in over 100 gross grafts.

Contrary to some reports, we find that these homografts "take" and vascularize in exactly the same fashion as autografts or isografts. The graft vessels again participate in the new circulation and the timing of the first blood flow is strikingly identical with that of autografts. Unless there is infection or gross technical failure, there is no evidence of thrombosis of the bed vessels beneath these homografts.

Homografts also elicit the same initial "sympathetic response" in the vessels of the bed that we find in autografting. Again, this often appears about 24 hours before the graft vessels begin to show circulation and subsides gradually over another 48-72 hours. Grossly, homografts turn pink in 48 hours when the open technique is used and

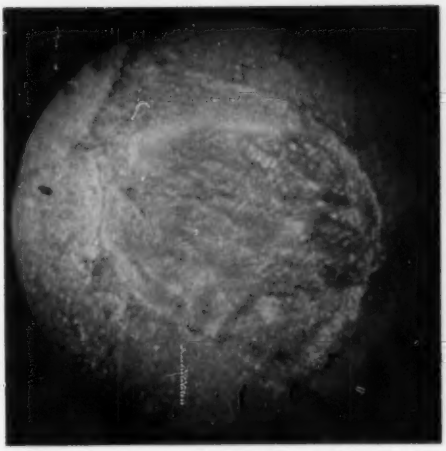

Fig. 4A.—Autograft six days after grafting (lighting from above); reduced approximately 1/3 from mag. × 6. The graft is pink at this stage except for the pale nonviable overlap around the margins. The small vessel running transversely is a graft vessel that now shows rapid corpuscular flow.

Fig. 4B.—Autograft six days after grafting (using transmitted light); reduced approximately 1/3 from mag. × 6. Transmitted light shows the crossing patterns of the two vascular networks. The finer transverse vessels are those of the graft. The larger vertical vessels are those of the host. Under the microscope at higher powers these two networks may be seen to join in several areas. Overlap of the skin graft produces the dark areas about the margins and shows the importance of removing dermis in the central region for observations

Fig. 4C.—Autograft nine days after grafting (lighting from above); reduced approximately 1/3 from mag. × 6. On the ninth day, even in the black and white photograph, it can be seen that the graft has more color and is more completely vascularized than in Figure 4A. The period of "sympathetic response" is present, and the vessels of both the host and graft are dilated and show active circulation. From this point on the graft will become somewhat paler as the tissue anoxia is overcome.

Fig. 4D.—Autograft nine days after grafting (using transmitted light); reduced approximately 1/3 from mag. × 6. Transmitted light shows that the vertical host vessels are now several times larger than in Figure 4B. Many more communications may now be found between host and graft vessels. Diffuse dark areas in the graft represent many fine graft capillaries that are now open and carrying the blood that causes the pink color seen in Figure 4C. In these autografts the original vessel pattern of the graft seems to persist indefinitely.

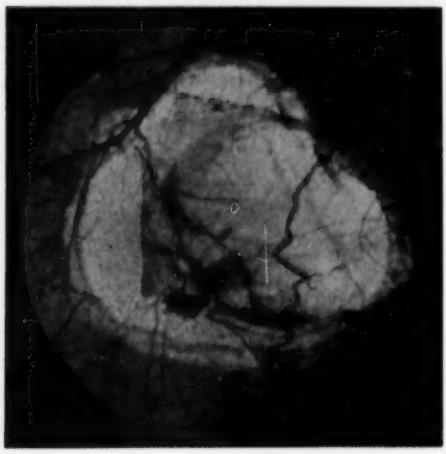

Fig. 5A.—Homograft 72 hours after grafting (lighting from above); × 6. The circular graft of ear skin occupies most of the field. The overlapping edges are pale and dry, but the graft is already pink, and the ear or graft blood vessel pattern may be clearly seen running from seven o'clock upward and toward one o'clock. Four or five main branches are seen, and one of these runs out into the graft overlap at three o'clock. The hyperemia and pink color are typical of the sympathetic response with initial vascularization.

Fig. 5B.—Homograft 72 hours after grafting (transmitted light); × 6. When transmitted light is applied to the chamber in Figure 5A, we can see the two crossing patterns of blood vessels. The larger host vessels enter the graft bed from three o'clock and nine o'clock. Rapid circulation is present in these vessels. The finer pattern of graft vessels seen in Figure 5A is also visible and runs vertically. The RBC and WBC in these vessels have also begun to circulate slowly. In several areas direct anastomoses have been established between the host and graft vessels.

Fig. 5C.—Homograft eight days after grafting (lighting from above); × 6. This graft is showing a mild hyperemia just prior to appearance of its rejection end-point. The graft is still vascularized except for the dry edges of overlap that are falling off. The ghost epithelial layer has been shed, and hair growth can be seen under higher magnifications. The healthy luster of the surface epithelium is typical, but the graft is definitely not as hyperemic as in Figure 5A.

Fig. 5D.—Homograft eight-plus days after grafting (transmitted light); × 6. When transmitted light is applied to this chamber we can see evidence of the rejection end-point in the rather sudden reduction in the caliber of the graft vessels (fine vessels running vertically). Higher magnification showed marked slowing of the flow in these vessels while the flow in the host vessels remained brisk. At this point, for the first time, an observer would be certain that this represented a homograft rather than an autograft.

Fig. 5E.—Homograft eleven days after grafting (lighting from above); × 6. Although vascular rejection began 48 hours earlier, this graft still looks reasonably viable. The presence of hemorrhagic areas such as that at four o'clock is warning of further breakdown in the days ahead. Note that the vascular pattern so clearly seen in Figure 5A is now almost completely gone, suggesting that endothelial necrosis preceeds epithelial necrosis.

Fig. 5F.—Homograft 11 days after grafting (transmitted light); × 6. Although this homograft is well along with rejection, there is no evidence of thrombosis in the vessels of the graft bed and circulation continues briskly in these transverse vessels. The graft vessel pattern, on the other hand, has altered markedly, and no circulation remains in most of these vertical vessels. The areas of ecchymosis seen in Figure 5E may now be recognized as areas of free red cell extravasation at the junction between the graft and the host bed. These hemorrhages seem to occur at points of previous junction between host and graft vessels.

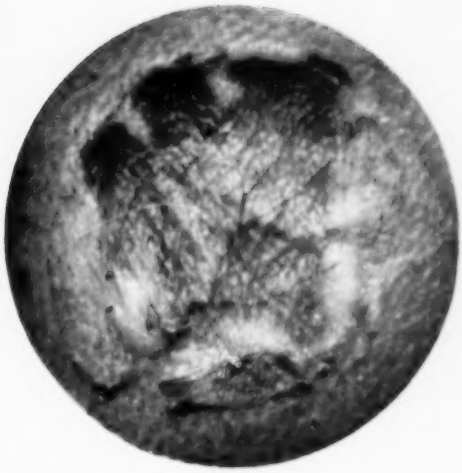

Fig. 5A

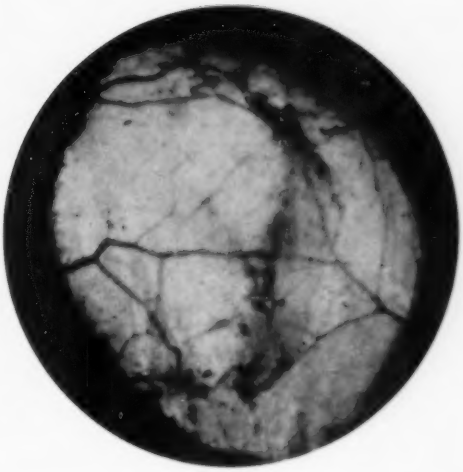

Fig. 5B

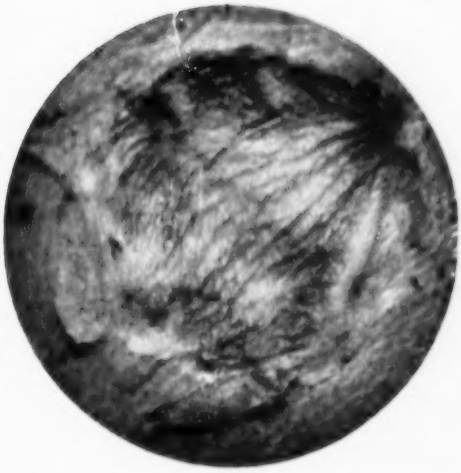

Fig. 5C

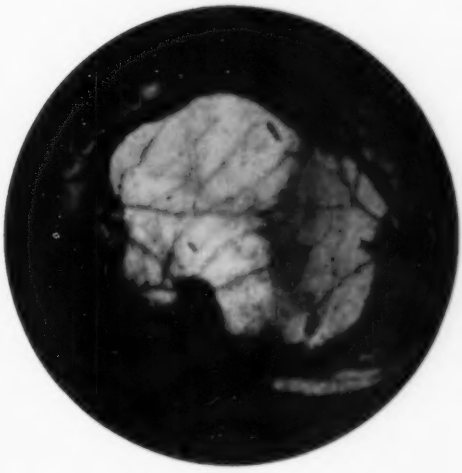

Fig. 5D

Fig. 5E

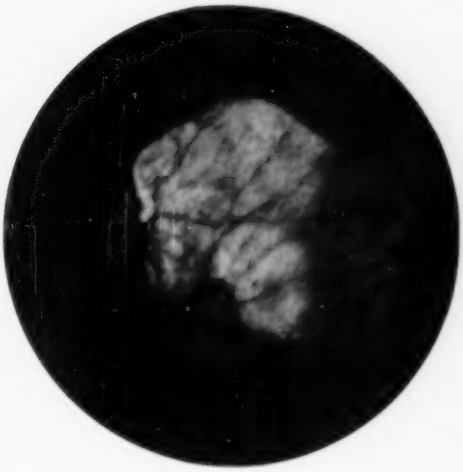

Fig. 5F

hair growth becomes obvious in 6 to 8 days. We find 100% ultimate failure of these skin homografts when carried out between two different inbred mouse strains. The late changes seen during failure of these grafts are also very intriguing and follow a definite, consistent pattern.

Usually on the eighth day after grafting, there is a definite increase in the size and number of vessels in the graft bed. This secondary vascular response is in every way similar to the initial "sympathetic response" observed just before circulation is seen in the graft. The graft then becomes grossly paler and the movement of RBC and WBC becomes slower in many of the graft vessels. Other vessels become smaller in caliber or even disappear. Sections of graft vessels may be seen with no circulation. These early changes of homograft rejection constitute a very dramatic and clear-cut end-point. This end-point may be defined as the sudden reduction in the caliber of the larger graft blood vessels accompanied by slowing of the flow rate in these vessels. Even though the period of actual sloughing of the entire graft may extend over many days, this microscopic end-point is quite specific and consistent. When skin grafting was carried out between the A-line and CBA mouse strains, this time of change was 9.0 days (plus or minus 12 hours) in more than 95% of all homografts. Beginning with this "rejection end-point," there is a progressive disorganization in the pattern of the larger graft vessels. Small hemorrhages may occur, but some of the smaller graft vessels may continue to have good circulation for an additional 10 to 14 days (See Figs. 5A-5F).

Gross grafting with much larger grafts showed exact reduplications of the signs of beginning failure as evidenced by dark spots of hemorrhage appearing under the grafts on the eighth or ninth day (Fig. 5). The chamber studies have established, however, that some appreciable flow of blood continues within the graft vessels occasionally for as long as 20 days after grafting. At no time during this period do the blood vessels in the host bed show thrombosis.

We have wondered about the so-called "dosage" phenomenon [6] and wished to determine whether the size of a first-set homograft would affect the violence or rapidity of its rejection. We tested this by carrying out gross grafting of large grafts between the same two species of mice, without the use of the chamber. Over 200 additional grafts were applied. These grafts were 25-30 times the mass of some of the chamber grafts. By using a completely open technique, we have been able to get consistently beautiful "takes" of full thickness grafts without the use of sutures or dressings of any type. The lack of pressure dressings makes it possible to follow changes in the grafts from the moment of grafting. Large skin grafts grossly became bright pink and showed circulation at the same time (48-72 hours after grafting) as their much smaller counterparts within the chambers. We do not find any evidence of a dosage phenomenon on first-set autografts or homografts. We hope to study the effect of "dosage" on second-set homografts in the future. Furthermore, these larger grafts made it clear that neither the small size of the chamber grafts nor other technical problems connected with transparent chambers, such as the presence of glass or mica, altered the timing of the observed vascular reactions.

Summary

These studies were designed to observe the detailed vascular morphology that accompanies skin grafting in mammals. The transparent chamber technique was modified to make it possible to study skin grafts under more physiological conditions. Over 300 autografts and over 300 homografts have been studied, with use of CBA and A-line inbred mouse strains. Additional visibility for observations within the chambers has been obtained by surgical insertion of a disc of optical glass beneath the bed of the graft.

The following results have been obtained:

1. Homografts and autografts show identical initial vascular responses during the period of "take."

2. The timing of these changes is the same for both autografts and homografts but may be influenced to some extent by the thickness of the grafts and the vascularity of the recipient bed.

3. Homograft rejection of skin begins on the 9th day (plus or minus 12 hours) after grafting between the CBA and A-line mouse strains. This rejection end-point is consistent and consists of sudden reduction in the caliber of the larger graft vessels, accompanied by slowing of the flow rate in these vessels.

4. This rejection end-point is almost invariably preceeded, 12 to 24 hours before, by a hyperemia or sympathetic response in the vessels of the host bed.

5. Attempts to determine length of homograft survival by waiting for apparent gross slough of all graft-tissue or cessation of all graft circulation will lead to widely varying results.

6. The "dosage phenomenon" does not apply to first-set autografts or first-set homografts of skin.

7. Unless sepsis is allowed to occur, the rejection of skin homografts is not accompanied by the development of thrombosis in the vessels of the graft bed.

8. The establishment of active circulation in any autograft or homograft is largely dependent on the actual end-to-end anastomosis of graft vessels with those of the host. This occurs in some cases as early as 48 hours after grafting.

9. Once the rejection of the homograft begins, the vascular pattern of the graft begins to disrupt and disappear rapidly. In the case of autografts, the pattern of graft vessels will persist as long as the experiments have been followed (over 12 months in some animals).

Dr. John D. DesPrez, Mr. John Boitnott, and Miss Marian Hanson helped in this work.

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Anomalies of the Urachus in the Adult Patient

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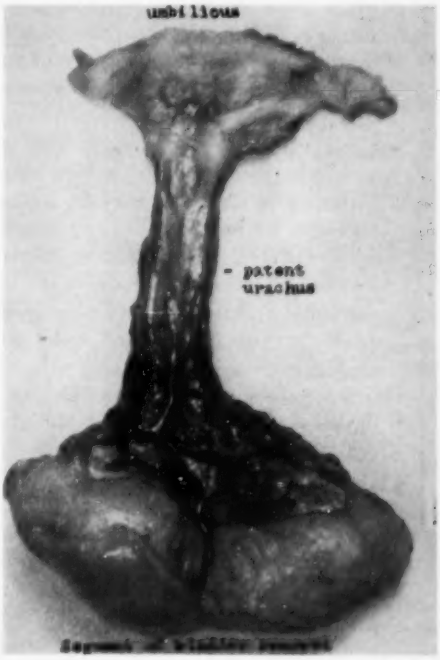
Anomalies of the urachus are occasionally encountered in surgical practice. Herbst [1] states that the earliest recorded case in the literature was reported by Cabral in 1550, but the first clear-cut description was by Tait [2] in 1886. Callanan [3] in 1951 summarized the cases since Dudgeon collected 154 cases in 1940. Individual cases have since been reported by Getz and Thomas [4] in 1950 and by Helsby [5] in 1955.

The human embryo at the six somite stage of development forms a cloaca which is a common receptacle for urinary and gastrointestinal waste products. The allantois develops at the cephalic end of the cloaca. This latter structure is a vestigial remnant which is intimately related with the development of the placenta and umbilical cord. The urachus (elongated apex of the bladder) is continuous with the allantois at the umbilicus. After birth, the descent of the urinary bladder to the retropubic position carries the urachus downward, and normally the connection with the umbilicus is obliterated. Begg [6] has emphasized that the urachus is lined by stratified squamous epithelium, which persists through life as nests of cells between the transversalis fascia and the peritoneum. Necrosis of these cell nests may occur, with resulting cyst formation. Only the abnormal urachus reaches the umbilicus; however, it has a contiguity with the umbilicus because of its intimate anatomical relationship with the umbilical arteries, which lend fibrous support from their adventitia. Lowsley and Kerwin [7] state that the extent of the normal urachus is one-third of the distance from the bladder apex to the umbilicus.

Failure of the normally patent fetal urachus to become obliterated results in anomalies which Long [8] has classified into four main groups:

1. Complete type. The urinary bladder is in direct communication with the umbilicus by means of a patent urachus. Discharges of urine from the umbilicus may be present, particularly on micturition. Figure 1 shows an example of this type in the specimen which was surgically removed.

Fig. 1.—Complete type of urachal anomaly. The patent fetal urachus did not obliterate, and the urinary bladder is in direct communication with the umbilicus.



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2. Blind external type. The urachus is open only at the umbilical end.
3. Blind internal type. The urachus is open only at the bladder end.
4. Totally blind type. The urachus is closed at either end, with resulting urachal cyst formation. At times, patency may be lost by superimposed infection.

In two-thirds of the cases the urachus is separated from the bladder by a transverse fold, which may be the reason for failure of communication to be demonstrated by cystoscopy and cystogram.

Symptoms may be grouped in the majority of instances into one of the following categories:

1. Asymptomatic. Campbell [9] reported 15 instances in his series of 12,080 autopsies on children.
2. Midline tumor formation. This often may be mistaken for a uterine mass. Downward traction on the mass may cause retraction of the umbilicus. In the blind internal type the tumor can at times be made to appear and disappear by alternate filling and emptying of the urinary bladder. We were able to demonstrate this phenomenon in one of our cases. In another an extrarectal mass was palpable on rectal examination.
3. Umbilical drainage. Drainage from the umbilicus is often a presenting complaint. The character may be serous, purulent, or urinary. Purulent drainage is the commonest type encountered, in view of the fact that secondary infection is frequent. Purulent drainage from the umbilicus should make one cognizant of the possibility of infected urachal remnant. A persistent omphalomesenteric duct should be ruled out by an appropriate sinogram.
4. Gastrointestinal symptoms. An infected urachal remnant can be mistaken for acute appendicitis or diverticulitis. Helsby's [5] case was diagnosed preoperatively as acute appendicitis, but at surgery a perforated urachal cyst with secondary peritonitis was found. Callanan [3] also reported a similar case. Sawyer [10] reported a case in which the x-ray findings were compatible with a diagnosis of diverticulitis, but at operation a fistulous communication between an urachal cyst and the sigmoid was found.

The complications of untreated urachal anomalies are calculus formation and infection. The infected urachal remnant can perforate into the peritoneal cavity or any of the nearby organs. The route of infection is not clearly understood, although a hematogenous route has been advocated. Infection of the urinary bladder may be an etiological agent, but in our cases urinalysis was within normal limits and only one-third of the reported cases communicate with the urinary bladder.

The treatment has been varied. Incision and drainage with application of silver nitrate locally, as well as marsupialization, has been advocated. We believe primary excision to be the treatment of choice. Gross [11] treated five cases by incision and drainage, but one case required subsequent excision of the mass. If abscess is present, we advocate incision and drainage with later total excision en bloc. If inflammation is present, it is treated and allowed to subside for several weeks before definitive surgery is attempted. If an internal communication with the urinary bladder is present, we believe that distending the bladder with 200 to 300 cc. of sterile saline solution prior to surgery will aid in outlining the pathology. If possible, it is wise to avoid entering the peritoneal cavity, but we were unable to do so because of previous inflammation which resulted in adherence of all layers. If the peritoneum is opened, a linear segment is removed. We do not believe it necessary to remove the umbilicus. A paramedian incision extending from the umbilicus to the pubis is the one of choice. If the urachal remnant is of the blind internal type with communication to the bladder, a segment of bladder should be excised and the edges inverted in two layers. The space of Retzius should be drained and an indwelling catheter

maintained for at least one week. Antibiotics should be used because of the high incidence of preoperative and postoperative infection.

Report of Cases

CASE 1.—A 26-year-old Negro man was admitted to Hines V. A. Hospital on June 11, 1955, with a history of chills, fever, burning on urination, and lower abdominal cramping pain, which had its onset 60 hours prior to admission.

Physical examination revealed an acutely ill patient with a temperature of 101 F. Lower abdominal tenderness, particularly in the midline, was elicited. The umbilicus was tender and injected. An umbilical opening admitted a probe for a distance of 1.5 cm. No umbilical drainage was noted.

The laboratory work-up revealed the urinalysis to be within normal limits. The hemogram revealed a white blood cell count of 14,900, with 70% neutrophils and 30% lymphocytes. Cystoscopy and cystogram revealed a patent urachus of the blind internal type.

Hospital Course.—The omphalitis was treated with penicillin and hot packs. After the infection had subsided the patient was operated upon. The urinary bladder was distended with 300 cc. of sterile saline solution, which was injected through the urethra prior to surgery by means of an indwelling catheter. Through a left paramedian "hockey stick" incision, the distended cyst was visualized and excised en bloc with the adherent peritoneum. The urachal sinus was demonstrated at surgery to be of the complete type. A segment of the dome of the bladder was removed, and the edges were inverted in two layers with chromic absorbable surgical (gut) sutures. The space of Retzius was drained, and the indwelling urethral catheter was left in place for one week. Postoperatively, a minor superficial skin infection developed, which responded to local heat and parenteral antibiotics. The patient was followed for seven months after discharge and was symptom-free.

CASE 2.—A 33-year-old white man was admitted to Hines V. A. Hospital on July 13, 1950, complaining of urinary drainage from the umbilicus during the act of micturition during the previous two to three weeks. A previous episode had occurred two years prior to admission, but it subsided spontaneously.

Physical examination revealed an afebrile patient who did not appear to be acutely ill. Periumbilical injection was present, with no umbilical discharge at the time of examination; however, lower abdominal guarding was present.

The laboratory work-up revealed the urinalysis to be within normal limits. The hemogram showed an elevated white blood cell count (16,400), with 79% neutrophils, and the other values were within normal limits.

Hospital Course.—The intravenous pyelogram was normal, as well as the cystogram. Even on voiding, no dye was seen to issue from the umbilicus. At operation, an urachal sinus extended from the dome of the bladder to the umbilicus. The bladder portion was closed by cicatrizing scar tissue. The umbilicus, urachal sinus tract, and a portion of the dome of the bladder were excised en bloc. The peritoneum was inadvertently opened because of adherent scar tissue. The bladder was closed around a Pezzer catheter. The space of Retzius was drained. Three days postoperatively, signs of peritoneal irritation developed, interpreted as mild peritonitis, which responded to two days of chlortetracycline (Aureomycin) therapy. This patient was followed for a period of 19 months with no evidence of recurrence.

CASE 3.—A 33-year-old white man was admitted to Hines V. A. Hospital on May 19, 1955, complaining of pain and discharge from the umbilicus with right lower quadrant cramps of five days' duration.

Physical examination revealed a white man who did not appear to be acutely ill, with a temperature of 99.8 F. The umbilicus was injected and swollen and was discharging seropurulent material. Tenderness and guarding about the umbilicus and right lower quadrant were present.

The laboratory work-up revealed the urinalysis to be within normal limits. The hemogram revealed an elevated white blood cell count (16,000) with 79% neutrophils, 20% lymphocytes, and 1% eosinophils. The small bowel and barium enema x-ray series revealed an incomplete rotation of the bowel, with no evidence of Meckel's diverticulum. The umbilical sinogram was compatible with a diagnosis of persistent urachal sinus, with no evidence of communication with the bladder. Cystoscopy and cystogram were normal.

Hospital Course.—The umbilical discharge subsided with the local application of hot wet packs and tetracycline therapy, given orally and intramuscularly. After the inflammation had subsided for a few weeks, definitive therapy was carried out. A midline "hockey-stick" incision was made, and an urachal sinus tract was found of the blind external type. The umbilicus was preserved, but the connection with the urachus was severed. At the lower end of this tract, firm adherence to the bladder was encountered, but there was no communication and therefore the bladder was not opened. The peritoneum was deliberately entered because of the firm adherency of the inflammatory scar tissue. The space of Retzius was drained, and the indwelling urethral catheter, which was placed preoperatively, was maintained. A wound

infection developed 10 days postoperatively, which responded to the local application of heat and parenteral antibiotics. The patient was discharged in an asymptomatic state.

CASE 4.—A 28-year-old white man was admitted to Hines V. A. Hospital on March 19, 1952, complaining of a painful swollen umbilicus of two or three weeks' duration. On two occasions there were dark umbilical discharges.

Physical examination revealed a white man who was not acutely ill, with a temperature of 99 F. The umbilicus protruded 0.5 cm. above the skin level, with a sinus opening at the inferior pole and a granulating area.

The laboratory findings revealed the urinalysis to be normal, as were the hemogram and small bowel x-ray series.

Hospital Course.—The local inflammatory process subsided after one week of local applications of heat and antibiotics. The umbilicus was excised through a double eliptical incision made horizontally. A persistent urachal sinus with two obliterated umbilical arteries was found. There was no connection with the bladder. This urachal sinus was of the blind external type. During the course of surgery, the peritoneum was entered. The postoperative course was uneventful. The follow-up was for a period of three months, with no evidence of recurrence of symptoms.

CASE 5.—A 32-year-old white man was admitted to Hines V. A. Hospital on Oct. 8, 1950, complaining of periumbilical and lower midline abdominal pain of two weeks' duration. Three days after the onset of pain, a thick malodorous discharge exuded from the umbilicus. A physician was consulted who prescribed local heat, penicillin, and sulfa drugs, with no effect.

Physical examination revealed a white man who was not acutely ill. The umbilicus was tender and injected, with foul-smelling fluid exuding from a sinus tract, which could be probed for a distance of 1.5 cm.

The laboratory findings revealed the urinalysis to be normal, as was the intravenous pyelogram. The white blood cell count was elevated (15,900 cells), with 77% neutrophils and 21% lymphocytes. The remainder of the hemogram was within normal limits. Culture of the umbilical discharge revealed anaerobic streptococci. Umbilical sinogram revealed a sinus tract extending for a distance of 1 in. (2.5 cm.).

Hospital Course.—After 13 days of treatment, which consisted of local heat and antibiotic therapy, the acute inflammatory stage subsided. The umbilicus was excised through a double elliptical incision made horizontally. An urachal sinus was encountered, which was excised with the attached peritoneum and was found to be attached to the dome of the bladder but not continuous with it. The postoperative course was uneventful.

CASE 6.—A 46-year-old white man was admitted to Hines V. A. Hospital on Jan. 5, 1955, complaining of having had low backache for a period of 10 years and a low midline abdominal pain for an indefinite period.

Physical examination revealed a white man who did not appear to be acutely ill and was afebrile. Tenderness was elicited in either flank as well as in the hypogastrium. The liver edge was palpable below the right costal margin. There was a decrease of motion of the neck to the left and upward.

The laboratory examinations revealed the urinalysis and the hemogram to be within normal limits. The serologic tests were normal, as were the liver-function tests. X-ray examination of the spine and kidneys did not reveal any pathological changes. Calculi were noted within the prostate gland. Cystoscopic examination revealed no pathological findings.

Hospital Course.—Consultation was had with members of the arthritic service, who thought that the low backache was due to chronic sprain. It was felt that his other symptoms were due to an appendiceal stump (following appendectomy at age 35) or to a patent urachal remnant. Laparotomy was accordingly advised. Under general anesthesia, through a right low paramedian incision, laparotomy was performed. An appendiceal stump which was not inflamed was found and removed. A patent urachal remnant was also found communicating with the dome of the bladder but ending 2 cm. below the umbilicus. This was of the blind internal type. The urachal sinus was removed with a section of bladder. The dome of the bladder was inverted in two layers with chromic gut sutures. The space of Retzius was drained in the usual manner, and an indwelling urethral catheter was maintained. The postoperative course was uneventful. At the six-week follow-up examination the patient was found to be asymptomatic.

CASE 7.—A 24-year-old white man was admitted to Hines V. A. Hospital on Jan. 12, 1950, complaining of an upper respiratory infection, constipation, dysuria, and low abdominal pain of three weeks' duration. One year previously the patient had had two previous episodes. Four days prior to admission he developed a firm tender swelling about the umbilicus, which developed vesicles with serous drainage. There was swelling and tenderness in the midline below the umbilicus.

Physical examination revealed a well-developed well-nourished white man who did not appear acutely ill and who was afebrile. The essential physical findings were a small amount of granulation tissue about the umbilicus, no drainage, and

a firm tender mass 3 by 4 in. (7.5 by 10 cm.) in size, below the umbilicus, in the midline, above the prostate, and apparently attached to the dome of the bladder.

The laboratory examinations revealed the urinalysis and the serologic tests to be within normal limits. The white blood cell count was 11,500, with 72% neutrophils, 27% lymphocytes, and 1% eosinophils. The remainder of the hemogram was within normal limits. Roentgen examinations of the chest and kidneys were normal. Cystoscopy revealed that the bladder was filled symmetrically, except in the dome, where it appeared that an extrinsic mass was bulging into the bladder. These findings were confirmed by cystogram.

Hospital Course.—The patient was treated with local moist heat, penicillin, and sulfadiazine. On this regimen, the umbilical drainage gradually subsided and the abdominal mass slowly receded to the size of a lemon, at which size it remained. Under general anesthesia, the umbilicus, urachal remnant, and a section of the dome of the bladder were excised, through a low midline incision. The patent urachus was of the complete type. The bladder defect was closed around a Pezzer catheter, and the space of Retzius was drained. Eleven days after surgery the Pezzer catheter and drain were removed and a Foley urethral catheter was inserted. The suprapubic sinus tract closed rapidly, and the postoperative course was uneventful. The patient was followed for a period of 36 months and was found to be asymptomatic.

CASE 8.—This case is summarized briefly to demonstrate the asymptomatic type. A 23-year-old Negro man was admitted to Hines V. A. Hospital on June 25, 1950, with right lower quadrant pain of 36 hours' duration. A diagnosis of acute appendicitis was made. At operation an acutely inflammed appendix was removed. A low midline mass was also seen. It was 2 in. (5 cm.) in diameter, in the region of the dome of the bladder. This urachal cyst was not removed. Postoperative work-up failed to reveal any connection of the cyst to either the umbilicus or the urinary bladder. This is an example of the totally blind type.

Comment

The most important point in diagnosis of an urachal anomaly is to keep this possibility in mind. An omphalitis or umbilical drainage should make one suspicious of an urachal anomaly, particularly when it is associated with lower midabdominal pain. The

Fig. 2.—Cystogram demonstrating urachal anomaly.

Fig. 3.—Patent urachus. The radiopaque material was injected through the opening at the umbilicus.

diagnosis is confirmed by visualization of the sinus or cyst by injection of radiopaque material thru the umbilicus or the bladder (Figs. 2 and 3). If the urachus fails to visualize, sometimes an extrinsic pressure defect is noted at the dome. Routine urinalysis offers little help, as all urinalyses were normal in our series. The injection of sterile methylene blue solution thru the umbilicus and observing an almost immediate passage in strong concentration is a diagnostic aid which will be of value in the complete type. Probably the most important view on x-ray examination is the lateral (Fig. 4).

Fig. 4.—Patent urachus (lateral view). The radiopaque material was injected through the opening at the umbilicus.

Summary and Conclusions

Eight cases of urachal anomalies are presented—three of the complete type, three of the external blind type, and one each of the blind internal and totally blind type.

An omphalitis or umbilical drainage should make one suspicious of an urachal anomaly.

The treatment of choice in urachal anomalies which are symptomatic is surgical excision.

Visualization of the urachal sinus or cyst by means of injected radiopaque material is of value in confirming the diagnosis.

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Practical Aspects of the Surgical Treatment of Breast Cancer

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Breast cancer is an ancient and elusive disease which has claimed its many victims in all walks of life, at almost every age, and from time immemorial. Generation upon rising generation of physicians and surgeons alike have challenged this malign and monstrously destructive disease, resorting to every conceivable treatment considered curative at the time. However, despite the tremendous strides of our healing art, breast cancer mortality has not yet reflected to any major degree the bountiful benefits of an ever-improving surgical skill.

Although the hope of hormones, endocrine ablation surgery, and radiotherapy have all added to our armamentarium in the total treatment of this disease, the benefits of these modalities of therapy are, thus far, purely palliative. Whereas the ultimate conquest of breast cancer will certainly be the triumph of the chemotherapist, virologist, or biologist, until then all of us must, by our present everyday practice, provide the best possible treatment for each individual patient.

Cancer of the breast appears to have world-wide distribution and is in truth an arrant "world citizen" whose cellular turmoil shows no special predilection for race, climate, or geographical distribution. Morbidity studies for the United States alone indicate that the incidence of breast cancer is higher than for any other specific primary site of cancer in either men or women. Among women it is the most frequent single organ to be attacked by malignant disease. It has been estimated that 5% of all women reaching adult life—one woman in twenty—will ultimately develop breast cancer. Almost 22% of all malignancy in women is due to this devastating disease, and it remains the commonest cause of death for women in that prime period of life between 40 and 60 years of age.

As noted by Steiner the curability of cancer today is dependent upon its being diagnosable, accessible, localized, and not involving organs essential to life. Certainly one of the most important of these considerations is the localized versus the disseminated disease. Although the breast is a readily accessible surface organ, less than two out of five cases of breast cancer are currently discovered while the tumor is still localized to the breast alone—before it has metastasized to the regional nodes (axillary or internal mammary) or beyond. It is readily apparent, therefore, that all of us must become increasingly alert to the dangers of this disease on less and less clinical evidence. Almost 2000 years ago Celsus observed that "only the beginnings of a cancer permit of a cure." Today, the wisdom of this observation merely emphasizes the need for earlier and still earlier cancer detection, diagnosis, and treatment. All of us must learn to find by physical examination alone those small and so-called "early" cancers which cast their shadows before them. By "early" I mean tumors which have produced their signs or symptoms only recently and are still amenable to definitive

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treatment. By careful breast examination we will find today what would be all too obvious tomorrow.

In a recent Hunterian lecture Riddell advises us "to accept with humility that, however experienced we are, we cannot differentiate with certainty on clinical grounds alone between non-malignant and early malignant" breast lesions. Thus, in this science of uncertainty the safest and surest diagnostic test for the discrete or solitary lump in the breast remains in my opinion surgical biopsy. This I prefer to the random probing of an aspirating trochar.

Today, some 60 years after Halsted set a new standard in the surgical therapy of malignant disease, the operative treatment of breast cancer has again reached a confusing state of doubt and dilemna. Haagensen and Stout have reawakened interest in the earliest admonitions of W. Sampson Handley, who in 1906 called for certain rather specific criteria of inoperability. With accumulated clinical experience all surgeons undoubtedly come to the realization that if the beginning is bad, the ending is worse. More lives are probably shortened by poor selection than by poor surgery. Although there is considerable diversity of opinion among surgeons regarding what constitutes correct "criteria of inoperability," yet few of us would disagree with Deaver, who said, many years ago, that "any operation, the purpose of which is merely to remove as much malignant tissue as possible, should be strongly condemned. Operations of this type contribute nothing to the comfort of the patient nor prolongation of life; on the contrary, the end is frequently hastened by exciting the disease to more active growth."

Now many surgeons discouraged by the present results of radical mastectomy are resorting to alternative modes of therapy. McWhirter, a resolute radiotherapist at the Royal Infirmary of Edinburgh, believes that more lives can be saved in unselected cases of breast cancer by simple mastectomy and intensive radiotherapy. On the other hand, Margottini, Wangensteen, Dahl-Iverson, Urban, and others are now fearlessly exploring the mediastinum and/or neck in a most extensive thoracic or cervical dissection known as the super-radical mastectomy. Theirs is the hope that "springs eternal in the human breast." This heroic surgery is the contemporary consummation of somatic reduction and its extension "is limited solely by the ability of the human remnant to survive." Some leading exponents of ultraradical surgery are seeking "second-look" operations, whereas, Park and Lees have recently suggested that it is doubtful if the survival rate is influenced by treatment at all. In commenting on our inability to control breast cancer mortality, McKinnon, a biostatistician, claims that "the failure of early treatment to reduce cancer mortality shows that spread of remote metastases occurs before surgical interference is possible."

It is undoubtedly true that all of us see too little and act too late, yet I am sure that it has been your clinical experience as well as mine that whereas breast malignancy "may be a milestone in the life of a patient, it need not be a tombstone." The biological behavior of breast cancer is all-important, and whereas most of us tend to celebrate our therapeutic triumphs when the degree of host resistance is high and the degree of malignancy is low, yet breast cancer is curable if treated in time. Radical mastectomy, in my opinion, remains the treatment of choice and should be performed in suitable patients as promptly as possible.

The latest review of our current results at The Johns Hopkins Hospital consist of a long term follow-up of all female patients with primary breast cancer—regardless of stage—who entered the hospital between 1941 and 1945. We have excluded from this study only those patients with recurrent disease, malignant melanomas, and breast sarcomas and males with cancer of the breast. There were a total of 259 patients, of whom the diagnosis of breast cancer was microscopically confirmed in 94%.

The absolute 5-year survival rate for all patients regardless of the type of treatment or the stage of disease was 37%, and the absolute 10-year survival rate was 23%. However, in those patients where the tumor was still localized to the breast alone—clinically or pathologically Stage I—the 5-year survival rate was 69%, and the 10-year survival rate was almost 50%. When the disease had spread to involve the regional nodes the 5-year survival rate fell rather sharply to 30% and the 10-year survival figure was only 16%. In patients with distant metastases or advanced disease there were no five-year survivors whatsoever. Thus, I think it is readily apparent to all that the stage of advancement of the disease at the time of original treatment is by far the most important single factor in predicting prognosis.

With regard to the surgical treatment of breast cancer, there were 185 patients out of 259 who were considered operable by means of radical mastectomy—an operability rate of 71%. The five-year survival rate for this group of patients treated by means of the classic Halsted type of operation was 46%. It might be added that the current practice at our hospital favors the use of postoperative radiotherapy in all postmastectomy patients with axillary metastases. Thus, many of these patients also received postoperative radiotherapy.

In this discussion of the practical aspects of the treatment of breast cancer, I would like to say a word regarding the technique of McWhirter, a very capable radiotherapist who has currently challenged our present complacency concerning radical mastectomy. This able Scotchman has advocated a most restricted type of simple mastectomy to be followed by a very carefully planned and personally administered course of intensive x-ray therapy. It must be emphasized, however, that simple mastectomy alone (without radiotherapy) has not been designed or recommended by McWhirter to replace radical mastectomy in the treatment of breast cancer.

The absolute survival rate reported by McWhirter is 42% for a 5-year period and 25% for a 10-year period. These statistics for simple mastectomy and very superior radiotherapy are remarkably good and compare favorably with those from major surgical clinics both here and abroad.

An excellent survey of McWhirter's results has been recently reported by Ackerman. Dr. Ackerman is not a surgeon or radiotherapist but an unbiased pathologist who was privileged to review this material while visiting Edinburgh a short time ago. He notes that despite a favorable five-year survival rate, many of the McWhirter patients are not really cured of their disease, residual carcinoma remaining in a relatively high percentage of patients. He also finds no histologic proof that radiotherapy sterilizes the regional lymph nodes and concludes from this and other evidence that simple mastectomy and radiotherapy have not been shown to be the treatment of choice in patients with operable breast cancer.

Now, on the other hand, the frequency with which metastases have been shown to occur in the internal mammary nodes, particularly in medial hemisphere lesions, has prompted some surgeons to extend the scope of radical mastectomy to include an en bloc dissection of the chest wall and internal mammary nodes. Margottini and Dahl-Iverson abroad and Urban and others in this country have made enterprising efforts to deal effectively with breast cancer which has spread beyond the reach of the conventional radical mastectomy. However, it remains to be seen whether the operative mortality and postoperative morbidity (and in the hands of Margottini and Urban this has been minimal) justify the strategy of superradical mastectomy. It is a matter of considerable importance to determine the limitations of ultraradical surgery—the point at which superradical mastectomy is nullified by the law of diminishing returns. However, early reports are, as yet, limited and incomplete but indicate that the survival rate is only slightly enhanced by extended radical mastectomy. Perhaps the indica-

tions and limitations of this type of heroic surgery must still await a longer test of time.

Among the important practical aspects of breast cancer, the complication of pregnancy is considered to be one of serious concern. Breast cancer occurring during pregnancy or lactation adds grave peril to the prognosis and should be treated by radical mastectomy and therapeutic abortion as promptly as possible. It has been my practice to caution all patients who have had breast cancer to avoid becoming pregnant for a postoperative period of at least three to five years, depending on whether axillary metastases were present at the time of operation or not.

In the total treatment of breast cancer the practical problem of the palliative care of the patient with advanced, recurrent, or metastatic disease must not be neglected. When the disease has spread beyond the reach of surgery, it is provident to resort to less specific measures of cancer control. Although hormone therapy is time-limited and unpredictable in its palliative effect, it is generally indicated for the widespread metastases which are so characteristic of advanced breast cancer. In deciding whether hormone therapy or x-ray therapy is to be regarded as the treatment of choice, one should select the method which is most likely to provide the patient with the greatest palliative benefit and relief of pain.

For the premenopausal patient the induction of an artificial menopause is certainly the initial endocrine alteration of choice. Clinical experience with the sex steroids indicates that the hormone of preference is based upon the physiological age of the patient in relation to her menopause. Androgen therapy is recommended for the premenopausal and postmenopausal patient, whereas estrogen therapy has been used most effectively in the older patient who is at least five years postmenopausal. Although the sex steroids are certainly not a "cure" for advanced breast cancer, they do offer a profound and gratifying palliative effect which often prolongs the period of comfort and survival.

With the recent increase of interest in the relationship between the endocrine environment and breast cancer, as well as with the increased availability of cortisone for effective substitution therapy, many clinical investigations have been undertaken recently to determine the effects of adrenalectomy, hypophysectomy, and intensive corticosteroid therapy in patients with advanced breast cancer. Time does not permit a review or rationale of these procedures, but I believe that it is fair to say that both adrenalectomy and hypophysectomy can be undertaken surgically without too great a risk and that objective regression will occur in a limited number (about 30%) of patients. However, as yet no satisfactory means for selecting patients who are most likely to respond to this type of radical endocrine ablation surgery is currently available. Tests for determining hormone dependent tumors have been suggested and are under careful clinical study. At present I favor the use of hypophysectomy or adrenalectomy only in those patients who have initially responded to castration and hormone therapy and who have now become refractory to these conservative measures.

In conclusion, therefore, I believe that it is well to be aware of the results and limitations of our present day treatment of breast cancer. For only with this doubt and uncertainty of our current knowledge will come the deepening of our insight into this problem. Although we have no reason to feel satisfied with our survival statistics, yet the fundamental principles of radical mastectomy must not now be abandoned in favor of either more conservative or more radical operative procedures. Despite these clinical experiments with newer techniques, the classic radical mastectomy is still a superior standard of surgical treatment, and, in the opinion of this observer, remains the operation of choice for most cases of breast cancer.

Experimental Meckel's Diverticulum

The Production of Peptic Ulcers by the Internal Drainage of a Heidenhain Pouch

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It has been shown that ulcers resulting from deviation of duodenal, pancreatic, and biliary secretions are due primarily to the corrosive action of undiluted and unneutralized gastric juice. A clear example of this corrosive effect is observed in those cases of Meckel's diverticulum containing heterotopic gastric mucosa with a peptic ulcer in the ileum adjacent to the entrance of the diverticulum. This corrosive action of gastric juice was demonstrated experimentally by Matthews and Dragstedt * by anastomosing Pavlov pouches to the ileum of dogs. Stoma ulcers occurred in 100% of the cases. A similar result was obtained by Barry and Florey,[3] working with cats and pigs. In the experiments of Gage, Ochsner, and Hosoi [4] ulcers occurred in only 71% of the animals when the Heidenhain pouches were constructed from the lesser curvature of the stomach. This can be explained by the greater acidity of the gastric juice secreted from the greater curvature, which is very rich in oxyntic cells. The secretion of gastric juice from a vagus denervated Heidenhain pouch is stimulated almost exclusively by the release of gastrin from the antrum of the stomach.

It has been demonstrated that removal of the antrum reduces permanently the gastric secretion from a Heidenhain pouch by approximately 90%. Transplantation of the antrum to the transverse colon as a diverticulum produces a hypersecretion of gastric juice of humoral origin since this hypersecretion may be demonstrated in a Heidenhain pouch. It seems probable that this hypersecretion is due to continuous and prolonged mechanical stimulation of the antrum by the intestinal contents and by motility.†

Experimental Procedure

Healthy, adult mongrel dogs were used for the experiments. The different experiments were performed as follows:

GROUP A.—Heidenhain pouches were prepared in dogs, and the pouch was drained into the ileum instead of to the exterior.

GROUP B.—Heidenhain pouches were prepared in dogs and drained into the ileum as before and in addition, the gastric antrum was completely excised.

GROUP C.—Heidenhain pouches were drained into the ileum, and the antrum of the stomach was transplanted to the transverse colon as a diverticulum.

All of the operations were performed with strict aseptic precautions and under general anesthesia induced with 2.5% thiopental (Pentothal) solution and continued with ether in a semiclosed circuit. Penicillin and intravenous fluids with occasional blood transfusions were given after operation. After recovery the animals were fed the routine laboratory diet of horse meat,

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From the Department of Surgery of the University of Chicago.

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* References 1 and 2.

† References 6-8.

Ulcer Production by Three Types of Internal Drainage

Group A, Heidenhain to Ileum			Group B, Heidenhain to Ileum Plus Antrectomy			Group C, Heidenhain to Ileum Plus Antrum to Colon		
Dog No.	Survival, days	Ulcer	Dog No.	Survival, days	Ulcer	Dog No.	Survival, Days	Ulcer
D-69	307	No	D-21	278	No	D-195	26	No
D-68	305	No	D-71	248	No	D-259	Alive	Yes
D-896	107	No	D-792	95	No	D-238	63	Yes (2)
D-898	105	No	D-720	95	No	D-132	50	Yes
D-889	100	No	D-779	90	No	D-131	13	Yes
D-1	125	Yes	D-751	90	No	D-214	9	Yes (2)
D-900	73	Yes						
D-927	30	Yes (3)						
8 dogs		3 ulcers	6 dogs		No ulcers	6 dogs		5 ulcers

bread, and milk. All of the dogs were observed daily until they died or were killed. Autopsies were made in all of the animals, and a careful inspection of the digestive tract was done. Microscopic sections and pictures were taken only where lesions were found.

Results

GROUP A (Heidenhain pouches drained internally to the midportion of the ileum).—Eight male dogs were operated upon in this group. Heidenhain pouches were made from the greater curvature of the stomach and anastomosed to the midportion of the ileum as a diverticulum. Three of the dogs died of peritonitis due to perforation of chronic ulcers near the anastomosis of the Heidenhain pouch to the ileum. In two of these animals, three additional ulcers were found in the ileum close to the Heidenhain pouch. Survival of these three animals was 30, 73, and 125 days after the operation. The five remaining animals were killed at 100, 105, 107, 305, and 307 days after the operation, and a normal gastrointestinal tract was found (Table).

GROUP B (Internally drained Heidenhain pouches to the midportion of the ileum plus excision of the gastric antrum).—Four female dogs and two male dogs were operated upon in this group. Heidenhain pouches of the greater curvature were made in the usual way and anastomosed to the midportion of the ileum. Resection of the gastric antrum was done at the same operation.

Fig. 1.—Photograph of a large ulcer in the ilium near the anastomosis with the Heidenhain pouch of the stomach.

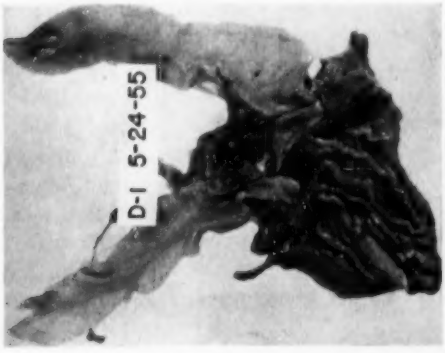
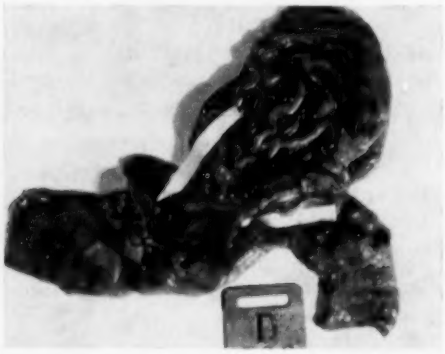


Fig. 2.—Photograph of a large perforating ulcer in the ileum near the anastomosis with the Heidenhain pouch of the stomach



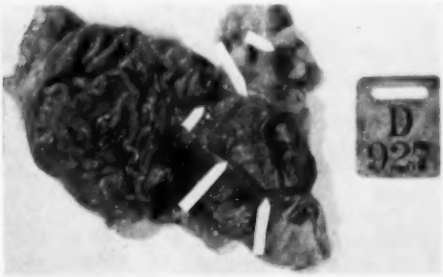


Fig. 3.—Photograph of a large ulcer in the ilium near the anastomosis with the Heidenhain pouch of the stomach.

Fig. 4.—Photograph showing the absence of ulceration in the ileum near the anastomosis with the Heidenhain pouch when the antrum of the stomach had been removed.

Continuity of the gastrointestinal tract was reestablished by means of a Billroth I type of reconstruction in four and Billroth II in two dogs. In one dog the antrum was transplanted to the diaphragm but at autopsy was found completely atrophic and replaced by scar tissue. All of the dogs were killed between 90 and 278 days after the operation. No ulcers were found in the gastrointestinal tract in the animals in this group (Table).

Group C (Internally drained Heidenhain pouches anastomosed to the midportion of the ileum plus transplantation of the gastric antrum to the transverse colon as a diverticulum).—Six dogs were operated upon in this group, three males and three females. Heidenhain pouches were constructed from the greater curvature in the usual fashion and anastomosed to the midportion of the ileum. The stomach was transected at the pylorus and at the junction between the body and fundus of the stomach. A Billroth I type of reconstruction was made. The pyloric end of the antrum was closed, and the proximal end was anastomosed to the transverse colon as a diverticulum. The blood supply of the antrum was carefully preserved. Three dogs died of peritonitis to perforation of chronic peptic ulcers in the ileum near the anastomosis with the Heidenhain pouch. These animals died 9, 13, and 50 days after the operation. One animal was reoperated upon 63 days later, and a large chronic peptic ulcer 3×4 cm. in diameter was found opposite the stoma of the internally drained Heidenhain pouch. A second ulcer 1.5 cm. in diameter was found in the jejunum close to the gastroenterostomy. One animal is still living, and one dog died of pneumonia 26 days after operation with no ulceration in the gastrointestional tract.

Comment

The results of this experiment support the view that typical peptic ulcers can be produced in the gastrointestinal tract by gastric juice secreted in response to the humoral stimulation of gastrin from the gastric antrum. In the experiments in Group A where the intestinal mucosa was subjected to the action of gastric juice normally secreted by a Heidenhain pouch, ulcers appeared in three of the eight animals. When the antrum phase of gastric secretion was hyperactive as in Group C, ulcers developed in four of the five dogs with one animal still living. When the antrum of the stomach was excised as in Group B and accordingly the antrum phase of gastric secretion was absent, no ulcers appeared in any of the six dogs operated upon. This fact shows once again that antrum stimulation and consequent gastrin release are the determining factors in the secretion of a Heidenhain pouch. An increase in the frequency and rapidity of ulcer formation was observed when the

antrum mechanism was hyperactive as in Group C. These findings offer a possible explanation of the fact that Meckel's diverticulum with ectopic gastric mucosa may produce immediate ulceration or that it may be present for years without ulcer formation, depending upon the activity of the gastric antrum.

Conclusions

1. Typical, chronic peptic ulcers are produced in dogs by the corrosive action of undiluted and unneutralized gastric juice when a Heidenhain pouch is anastomosed to the ileum and when the antrum mechanism is acting normally or when the antrum is overstimulated.

2. Excision of the antrum prevents the formation of stoma ulcers in the ileum of an internally drained Heidenhain pouch because there is no liberation of gastrin to stimulate the secretion of gastric juice.

3. When the gastrin mechanism is hyperactive as occurs when the antrum is transplanted to the colon, a hypersecretion of gastric juice from the internally drained Heidenhain pouch occurs and the frequency and rapidity of ulcer formation increases.

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Antibiotic Therapy

Treatment of Infectious Complications of Surgery of the Gallbladder and Bile Ducts

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Infections sometimes complicate operations on the gallbladder and bile ducts and require prompt and effective treatment. The purpose of this paper is primarily to outline the antibiotic treatment of such infections and to report the observations made in a number of cases encountered at the Mayo Clinic.

Principles of Antibiotic Treatment

The principles of successful management of infections complicating operations on the gallbladder and biliary ducts include (1) identification of the causative organisms when possible, (2) restoration of any hematologic and metabolic deficits and correction of any other condition that predisposes to continued infection, (3) elimination of factors preventing drainage of the wound and free access of antibiotic agents to the site of infection, and (4) careful selection and rational administration of antibiotic agents.

The principles of antibiotic therapy may easily be abused. If treatment with antibiotics is effective, it almost always is rapidly so, when given correctly. It is usually futile to administer these agents for prolonged periods in the hope that closed-off abscesses and similar lesions will disappear; rather, the surgical condition should be corrected early so that antibiotics are given maximal opportunity to be effective.

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Bacteriologic studies, including in vitro inhibition tests, are essential because the flora inhabiting wounds and abscesses secondary to operations on the gallbladder and bile ducts is mixed in about half of the cases. Pyogenic cocci and coli-aerogenes organisms are the usual invaders. Treatment of mixed infections is usually more complex than that employed for monobacterial infections, and elimination of some members of a mixed flora sometimes permits a surviving antibiotic-resistant species to colonize the lesion. Also, treatment with antibiotic agents must not be discontinued too soon; if it is, residual bacteria may be responsible for subsequent flare-ups.[1]

Although the treatment of infectious complications of biliary operations with antibiotic agents has given excellent results in many respects, it does not represent an unmixed blessing, because (1) it often entails extensive and highly technical bacteriologic study, (2) it may distort the signs and symptoms of infection beyond recognition before the diagnosis has been completed, (3) it may cause the emergence of micro-organisms that are resistant to the antibiotics being given, and (4) it may produce untoward reactions in some patients.

Selection and Administration of Antibiotic Agents

Members of the penicillin group of antibiotics are particularly effective against streptococci but less effective against micrococci. Penicillin V given in amounts of 200,000 to 500,000 units every four to six hours is dependable when the patient can take medicine by mouth and when the

organism is very sensitive to penicillin.[2] Penicillin G should be given parenterally in fairly large amounts, probably a minimum of 2,000,000 units a day, to control infection with Streptococcus faecalis, which is usually fairly resistant to the penicillins. In such infections even larger amounts of penicillin G along with one of the streptomycin group given in amounts of 1 to 2 gm. daily by the intramuscular route may be necessary.

Because of the ability of the streptomycin[3] drugs (streptomycin, dihydrostreptomycin) to produce a bactericidal effect, they are frequently used in combinations with other antibiotics in an attempt to produce synergistic killing of bacteria. Also, an organism that may be resistant to one or more antibiotic agents when used singly may not be resistant to a combination of drugs. Furthermore, the synergistic action of combined therapy may eradicate the infection more rapidly, thereby avoiding the necessity for prolonged use of a streptomycin drug. In addition, combined therapy theoretically may delay the onset of bacterial resistance. If hepatic function is normal, streptomycin is concentrated in the liver and excreted in the bile.[4]

The streptomycin drugs, however, tend to have toxic effects on the eighth cranial nerve, the incidence of which is directly proportional to the size of the daily dose and the number of days it is administered. In the absence of any renal damage, neurotoxic effects are not likely to occur if no more than 2 gm. of the drug per day is given intramuscularly for no longer than 12 to 14 days.

The members of the tetracycline group of antibiotics[3] are particularly effective against Gram-negative bacteria. In vitro inhibition tests indicate cross resistance among chlortetracycline (Aureomycin), oxytetracycline (Terramycin), and tetracycline; that is, organisms that are highly resistant to any one of these agents are almost always resistant in about the same degree to each of the other two. On the whole, these agents are interchangeable as far as clinical application is concerned; however, evidence suggests that concentrations of tetracycline in blood serum, and thus presumably in body tissues and fluids, are higher and of longer duration than with the other two agents.

The recommended dose of the tetracycline drugs for oral administration to adults is 500 to 750 mg. given every six hours. For patients who are critically ill, 0.5 gm. may be administered intravenously every 6 or 12 hours. These drugs may also be administered by the intramuscular route, which provides adequate serum concentrations of them; the recommended dose for adults is 100 to 200 mg. every six to eight hours.

The tetracycline agents are concentrated in the liver and are excreted in rather large amounts in the bile, the quantity in the bile being as much as 8 to 16 times that in the blood stream. Thus, these agents are extremely useful in the treatment of infections of the biliary tract, if the function of the liver is not too greatly deranged.

Aside from the fact that chloramphenicol[3] is more effective than other antibiotics against some micrococcal infections, it usually has no advantage over the tetracycline drugs in the treatment of infections following biliary operations. Since it may have a suppressive effect on the bone marrow, it should be used only when less potentially toxic antibiotics have failed or are contraindicated.

Neomycin[3] has rare application in the treatment of infectious complications following operations on the biliary tract; it may be used occasionally in micrococcal enterocolitis and less frequently in infections with resistant Gram-negative bacteria. Its toxic effect on the eighth cranial nerve as well as the renal irritation it causes when used systemically limit parenteral use of it. It can be used orally with almost complete freedom of concern, since it is not absorbed when given by that route. If neomycin is used systemically, the dose should not ex-

ceed 250 mg. given every six hours, and it should be injected intramuscularly.

Bacitracin [3] may act synergistically with penicillin against Gram-positive cocci, but it is nephrotoxic and requires careful studies of renal function. If bacitracin is used systemically the recommended dose is 10,000 to 20,000 units given intramuscularly four times a day. Very little of it is absorbed after oral administration, and we have used it successfully in this manner in the treatment of resistant micrococcal enterocolitis.

Polymyxin B (Aerosporin [3]) has constant clinical application at present only in infections caused by Pseudomonas organisms; utmost caution must be exercised in its use. The daily dose for adults is 100 to 200 mg. divided into four doses and given intramuscularly. It is not absorbed from the gastrointestinal tract and has been used as an intestinal antiseptic. It frequently causes pain at the site of injection; it may be responsible for cerebellar ataxia, and, like streptomycin, it may produce acral and circumoral paresthesia. Like neomycin and bacitracin, it is nephrotoxic, and the value for blood urea should be watched closely when it is being used.

Erythromycin [5,6] has proved effective against strains of micrococci, but the number of resistant strains seems to be increasing. The smallest dose that will maintain adequate serum concentrations is about 300 mg. given orally every six hours. More than 500 mg. by mouth often produces signs of gastrointestinal irritation, including nausea, vomiting, and occasional diarrhea. Preparations for parenteral administration are available. It is excreted readily in the bile.

Novobiocin [7] is a new antibiotic that appears to be effective against micrococci. It is administered orally to adults in amounts of 250 to 500 mg. every 6 to 12 hours. Preparations of the agent are available for parenteral administration. It is excreted readily in the bile.

Antibiotic Treatment in the Absence of in Vitro Sensitivity Tests

Treatment should always be based on the results of in vitro sensitivity tests whenever possible, and frequently these tests are an indispensable part of proper antibiotic therapy. However, facilities for the tests are not universally available, and even when they are available the time elapsing between the detection of postoperative infection and the acquisition of the results of such tests is often too long to permit delay of therapy. Under these circumstances, it may be advisable to start treatment at once with what appears to be the indicated antibiotic agent or agents and then modify the treatment, if necessary, when the results of sensitivity tests become known. This procedure often makes it possible for a seriously ill patient to be provided with adequate antibiotic therapy 24 to 48 hours sooner.

Generically speaking, postoperative infections due to streptococci are usually combated best with the penicillins. One of these agents alone is probably adequate for treatment of very sensitive strains, but for a resistant strain (S. faecalis) a streptomycin drug should probably be given also.

For postoperative micrococcal infections one must be cautious about considering any one agent as the drug of choice, because micrococci demonstrate remarkable ability to develop resistance to various antibiotic agents. The sensitivity of micrococci to a particular antibiotic appears to be largely a function of the total amount of the antibiotic currently being used in the area. For example, after four years of therapy with erythromycin more than 15% of the strains of micrococci isolated from patients hospitalized in Rochester, Minn., resist the action of that agent. Approximately 50% of the strains of micrococci resist the tetracycline and streptomycin groups of agents. One is reluctant to employ such toxic agents as chloramphenicol, bacitracin, neomycin, and polymyxin B routinely in micrococcal infections, even though most micrococci are sensitive to the action of these drugs. Novo-

biocin, recently introduced as an effective antimicrococcal agent, is currently much favored, but it seems likely that large-scale use of the agent will also eventuate in a progressive increase in strains capable of resisting the drug.

In more than minor postoperative infections due to Gram-negative bacteria of enteric origin, except Pseudomonas organisms, it may be best to proceed with combined tetracycline-streptomycin therapy. Neither a tetracycline nor a streptomycin drug alone is likely to control all Gram-negative infections, again because of the problem of resistance. Also, when these organisms demonstrate the ability to resist either type of agent alone, they may be eradicated by the synergistic effect of such combined therapy. Polymyxin B is the drug of choice in serious postoperative infections due to Pseudomonas organisms.

In mixed infections due to both Gram-positive and Gram-negative organisms and when the presence of an infection seems probable but bacteriologic investigation is impossible, it may be necessary to give several antibiotics simultaneously. Thus, one might give large doses of penicillin together with streptomycin in an attempt to eradicate S. faecalis and simultaneously give a tetracycline compound in an attempt to eliminate coli-aerogenes organisms. Needless to say, however, one attempts to keep the number of antibiotics used to a minimum.

We emphasize that these schemata should not be misconstrued as possible substitutes for in vitro sensitivity tests. We are aware that use of in vitro sensitivity tests does not cloak one with infallibility, that the method employed in testing is extremely important in assessing the reliability of the result, and that the tests will never replace clinical judgment. Notwithstanding, it is not possible to give the patient afflicted with a serious postoperative infection the maximum in good medical care without the use of adequate laboratory criteria.

Unnecessary Use of Antibiotics

We would caution against the tendency to use the antibiotics at the first sign of a fever in the postoperative patient. Unnecessary and indiscriminate use of these agents may induce a hypersensitive state which will disallow their use in the future when otherwise they might be lifesaving. The toxic properties of the antibiotics should always be weighed seriously before the agents are used. We should frequently recall that the advent of antibiotics did not bring about the demise of bacteriology, but rather, magnified its importance.

Observations on Mayo Clinic Series of Cases

With the primary purpose of providing additional data on the effectiveness of antibiotics in the treatment of infectious complications of operations on the gallbladder and bile ducts, we reviewed the records of some 11,500 patients who had undergone such operations at the Mayo Clinic from January, 1948, through December, 1954, and selected for detailed study the records of patients who had an infectious complication or a condition that could be confused with such a complication postoperatively (Table 1). Infections of the urinary and upper respiratory passages, because of the general prevalence of such infections, were not included in this study. A summary of the observations made in this study follows.

In general the clinical features of these infections were not unusual. The temperature ranged from 100 to 106 F in the majority of cases. Chills were not infrequent at the apparent onset of the complication.

TABLE 1.—*Infectious Complications of Operations on the Gall Bladder and Bile Ducts*

Complication	Patients
Wound infection	122
Pulmonary complication	69
Subhepatic and subdiaphragmatic abscess	44
Cholangitis	37
Micrococcal enterocolitis	4
Parotitis	3
Bacteremia	
Without other complication	2
With other complication	2
Wound dehiscence	2

TABLE 2.—*Bacteriologic Data Concerning Bacterial Resistance to Various Antibiotics in Sixty-Three Patients with Infection of the Surgical Wound*

Organism	Patients	Organisms* Not Inhibited by				
		Penicillin†	Tetracycline‡	Erythromycin§	Streptomycin‖	Both Streptomycin and Tetracycline
Micrococcus pyogenes	31	15	4	3	4	11
Coli-aerogenes	37		5		8	1
Streptococcus faecalis	16	5				
Pseudomonas aeruginosa	7		1		1	4
Proteus	6				1	2
Neisseria catarrhalis	1					
Alcaligenes faecalis	1					

Mixed infection, 33; apparently monobacterial infection, 30

* Remaining organisms were sensitive to the action of the indicated antibiotic.
† 10 units per cubic centimeter.
‡ 6.2 γ per cubic centimeter.
§ 3.2 γ per cubic centimeter.
‖ 25 γ per cubic centimeter.

Some malaise was present in all patients, while anorexia, headache, and sweating were present in many. Cough and thoracic pain were the rule in patients with pulmonary complications. Although cough was common also in victims of subhepatic and subdiaphragmatic abscess, upper abdominal pain and distress with deep respiration were more frequent. Jaundice and a spiking type of temperature curve were seen frequently in patients with cholangitis. The pulse rate was usually elevated in proportion to the fever. Leukocytosis occurred in most cases.

Wound Infections. — Infection of the wound, which developed in 122 cases, was the most frequent complication. Bacteriologic data concerning bacterial resistance to various antibiotics accumulated on 63 of the 122 patients are given in Table 2. Although cultures taken by swab or by aspiration from open wounds do not always give reliable information, they often can be of help in formulating a tentative therapeutic program. Micrococcus pyogenes was most frequently responsible for monobacterial infections (11 wounds) and, in association with enteric organisms, usually coli-aerogenes bacilli, was most frequently isolated in mixed infections (22 wounds).

All but 2 of the 122 infected wounds healed rapidly after administration of the appropriate antibiotic. One wound infected with both Escherichia coli and Pseudomonas aeruginosa required incision and drainage of a localized abscess, and one infected with M. pyogenes continued to drain for a year before it finally healed. The antibiotics were administered for variable periods, the average being six days.

Pulmonary Complications. — Of 69 patients who had a pulmonary complication exclusive of pulmonary embolism, 3 also had infection of the wound. No attempt was made by us to distinguish pneumonitis from atelectasis, since many patients in the postoperative state likely are afflicted with elements of each. Twenty-nine of the patients underwent procedures that were more prolonged and complicated than cholecystectomy. Bacteriologic data were of little help in differential diagnosis of the pulmonary complications and usually were not relied on in determining the antibiotic therapy to be used, since cultures of sputum in these cases frequently grow out organisms that are considered to represent members of the normal flora of the mouth and throat. No patient died of pulmonary complications. The contention that the majority of pulmonary complications are associated with contiguous spread of inflammation from the field of operation is perhaps supported by the fact that in 57 patients the right lower lobe of the lung was involved.

Subhepatic and Subdiaphragmatic Abscess.—Of 44 patients who had a subhepatic or subdiaphragmatic abscess, 10 had pulmonary complications that affected the right lower lobe, 6 being pleural effusions; cultures of the pleural fluid grew out coli-aerogenes organisms in all 6 cases and also S. faecalis in 2 cases. M. pyogenes was cultured from the blood in two cases and E. coli in two. Proteus was cultured in one of five cases in which bacteremia was associated with the abscess.

The abscess was incised and drained in 28 cases, and it drained spontaneously in 3. Fever due to the abscess had its onset between the 5th and 10th postoperative days in more than half the patients, although sometimes the basis for it was not apparent for several days.

Enteric organisms were most commonly cultured from the 31 abscesses that drained; members of the coli-aerogenes group predominated, although micrococci were identified in about one-third of the cultures. Mixed infections were present in two-thirds of the cases. Use of antibiotics in general was correlated with the results of in vitro inhibition tests.

Death occurred in only one case, in which postmortem examination disclosed pancreatic necrosis. One abscess recurred a year after apparent resolution.

Cholangitis.—Thirty-seven patients were adjudged to have cholangitis on the basis of preoperative fever not otherwise explained and on the basis of obstruction of the biliary tree and associated findings substantiated at operation. No patient in this group had associated multiple abscesses of the liver. Two patients had pulmonary complications in the right lower lobe; in one of these, empyema developed, and from the fluid E. coli was cultured repeatedly. Bacteremia due, respectively, to M. pyogenes and E. coli developed in two patients. One patient had a wound infection from which coli-aerogenes organisms were cultured.

Cultures obtained at operation from the bile ducts of two patients grew M. pyogenes. Various enteric bacteria, including coli-aerogenes organisms, Proteus, and S. faecalis, were reported on the cultures from the bile ducts of 27 patients; P. aeruginosa was cultured in only one case. In about one-third of the cases the infections were monobacterial.

Again, the selection of the antibiotic was dictated in general by the results of in vitro inhibition tests. There was only one death in the immediate postoperative period, this occurring on the fourth postoperative day. Two patients had recurrences of biliary stricture a year later. Two of the three patients with neoplastic obstruction of the bile duct are known to have died.

Other Infections.—Four patients had postoperative micrococcal enterocolitis.[8,9] Micrococci isolated from the stools were sensitive to erythromycin in two of these patients and to neomycin in the other two; treatment with the respective antibiotics coincided with prompt subsidence of the enterocolitis.

Parotitis developed in three patients, but in none did the complication progress to abscess formation.

E. coli bacteremia [10] developed in two patients, and recovery followed combined streptomycin-tetracycline therapy. Seven additional patients in whom bacteremia developed in association with other complications have been included in other groups.

Epididymitis developed in two patients on the second postoperative day.

Noninfectious Febrile Complications.—Dehiscence of the wound occurred in nine patients. In two there was definite evidence of an infectious basis for the dehiscence, as M. pyogenes was cultured from an associated purulent drainage in one case and S. faecalis was cultured in the other. However, for ease of presentation these two patients are not considered separately from the seven whose dehiscence apparently was not initiated by infection. None of the nine patients died.

Acute gouty arthritis became apparent in four patients within the first postoperative week. Transfusion reactions occurred in two patients.

Hypersensitivity to penicillin was manifested in one patient by urticaria and a temperature of 102 F. The reaction quickly subsided after use of the agent was discontinued and an antihistamine preparation was administered.

Fever of undetermined origin was present postoperatively in 18 patients who are mentioned here for the sake of differential diagnosis and because fever is usually associated with the recognized infectious complications. Extensive investigations did not establish a basis for the fever.

Summary

Infections that sometimes complicate operations on the gallbladder and bile ducts usually can be treated effectively. Such treatment entails (1) identification of the causative micro-organism and the selection and administration of the appropriate antibacterial agent, (2) elimination of factors that prevent drainage of the wound and free access of antibacterial agents to the site of the wound, and (3) correction of any condition, such as a hematologic or a metabolic defect, that predisposes to continued infection.

The principles of antibiotic therapy often are abused. When such therapy is effective it almost always is rapidly so, if given correctly. It is futile to administer antibiotics for prolonged periods in the hope that such lesions as closed-off abscesses will disappear; rather, correction of the surgical condition should accompany treatment with antibiotics. There should be no hesitancy in using antibiotic agents when they are definitely indicated, but the tendency to use them indiscriminately at the first sign of a fever in the postoperative patient should be avoided because their use may induce untoward reactions in some people and may cause the development of bacterial resistance.

The commoner infections following operations on the biliary tract at the Mayo Clinic for the period 1948 through 1954 were infection of the wound, pulmonary "infection," subhepatic and subdiaphragmatic abscess, and cholangitis. Less common infections were micrococcal enterocolitis, parotitis, infection associated with dehiscence of the wound, Epididymitis, and bacteremia with or without another complication. Noninfectious febrile conditions that had to be distinguished from those of infectious origin were dehiscence of the wound, acute gouty arthritis, transfusion reaction, and allergy to penicillin.

Mayo Foundation.

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Quantitative Studies on the Effect of Gastric Resection on Secretion of Gastric Juices

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The current surgical treatment of duodenal ulcer emphasizes subtotal gastric resection. The aim of this operation is the reduction of the acid-secreting capacity of the stomach, and, indeed, a large experience has shown that following subtotal resection the vast majority of duodenal ulcers heal. A quantitative relationship, however, between the amount of stomach removed and the secretion of acid gastric juice has never been shown. Histologic studies of the stomach have revealed a decrease in the number of parietal cells in the upper part of the fundus and in the cardiac region.[1] Common practice is to remove the lower 75% of the stomach, but does this result in a 75% drop in secretion? Evidence against such a direct relationship is the very high fasting gastric secretion occasionally seen in duodenal ulcer patients who have previously been subjected to subtotal gastrectomy and have subsequently developed stomach ulcers. This hypersecretion of the gastric remnant has been shown to be usually of nervous origin, because subsequent vagotomy reduces the secretion to a normal or subnormal level.[2]

It seemed worth while, therefore, to study the secretion of the innervated stomach as measured fractions of the fundus were removed. An ideal preparation for such a study appeared to be an innervated total stomach pouch with the antrum excised. This pouch was then subjected to repeated resections during which the vagus nerves were carefully preserved. It was presumed that the secretory characteristics of the pouch might reflect the acid production in patients with various degrees of partial gastric resection.

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From the Department of Surgery of The University of Chicago.

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Methods and Plan of the Experiment

Vagus innervated stomach pouches were prepared by the method of Dragstedt and Ellis[3] except for the antrum being excised. Gastrointestinal continuity was reestablished with esophagoduodenostomy. Following recovery from the operation, the animals were fed a daily diet of horse meat and kennel mix and 300 cc. of milk. Electrolyte balance was maintained by the addition of NaCl to the food. All of the animals in this series remained in good health and for the most part maintained their preoperative body weights. Quantitative 24-hour collections of gastric secretions were made in rubber football bladders attached to Stainless Steel gastric cannulas. The free acid was titrated with use of Topfer's reagent, and the results were expressed in clinical units of free acid. The HCl output in milliequivalents was calculated by multiplying the volume in liters by the free acid in clinical units.

The secretory characteristics of each animal were studied quantitatively in three ways after each pouch resection. First, the daily 24-hour secretions were collected for at least 30 days; second, the mean response of the pouch to a given amount of insulin was measured; third, the mean response of the pouch to a given amount of histamine was studied. The data from these three study methods will be presented separately as Parts I, II, and III.

When the control studies were completed as described above on the innervated fundic pouches, the lower quarter was resected from the pouch and the control studies were done again. In a similar way, the remainder of the pouch was resected in two more stages (Fig. 1) and secretory studies were repeated.

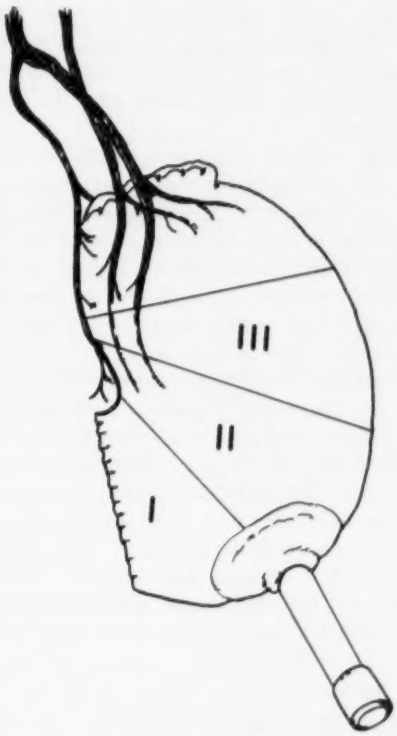

Fig. 1.—Graded resection of a total innervated fundic pouch.

Immediately after each resection of the pouch, the gastric mucosa was dissected from the specimen and was weighed while fresh. Thus it was to be established if there was a relationship between the weight of the gastric mucosa removed and the secretion. In the final operation, the remaining pouch was removed and the mucosa weighed. The total weight of the original mucosa was then obtained by adding up the weights of the mucosa from the several operations (significant regeneration was discounted). The data collected when the pouch was intact are expressed as gastric secretion with 100% of the fundic mucosa present. Then, after each resection, the data are expressed in terms of the percent of mucosa remaining.

Results

Part I. The Effect of Graded Resection on the Twenty-Four-Hour Daily Secretion from the Innervated Fundic Pouch.—Review of the data in Tables 1a to 1f show that a graded resection of the fundus of

TABLE 1a.—*The Effect of Graded Resection on the Mean Twenty-Four-Hour Daily HCl Secretion from the Innervated Fundic Pouch in D-315*

	Fundic Mucosa Present		HCl Secretion		
	Wt., Gm.	% of Total	mEq.	% of Control	Samples, No.
Total fundic pouch	115	100	43	100	102
Fundic resection I	88	76.5	40	93	34
Fundic resection II	55	47.8	20	46.5	50
Fundic resection III	34	29.6	20	46.5	38

TABLE 1b.—*The Effect of Graded Resection on the Mean Twenty-Four-Hour Daily HCl Secretion from the Innervated Fundic Pouch in D-425*

	Fundic Mucosa Present		HCl Secretion		
	Wt., Gm.	% of Total	mEq.	% of Control	Samples, No.
Total fundic pouch	42.5	100	19.0	100	30
Fundic resection I	30	70.7	13.0	68.5	37
Fundic resection II	17.5	41.2	8.8	46.8	50

TABLE 1c.—*The Effect of Graded Resection on the Mean Twenty-Four-Hour Daily HCl Secretion from the Innervated Fundic Pouch in D-626*

	Fundic Mucosa Present		HCl Secretion		
	Wt., Gm.	% of Total	mEq.	% of Control	Samples, No.
Total fundic pouch	92.5	100	58.0	100	48
Fundic resection I	59.5	64.5	31.0	53.5	40
Fundic resection II	Died postoperatively*				

*Dog—626 died of pneumonia postoperatively after the second fundic resection.

TABLE 1d.—*The Effect of Graded Resection on the Mean Twenty-Four-Hour Daily HCl Secretion from the Innervated Fundic Pouch in D-647*

	Fundic Mucosa Present		HCl Secretion		
	Wt., Gm.	% of Total	mEq.	% of Control	Samples, No.
Total fundic pouch	60.3	100	64.0	100	37
Fundic resection I	40.3	67	19.0	29.2	45
Fundic resection II	20.8	34.6	14.2	21.7	99
Fundic resection III	14.0	23.2	9.3	13.9	39

TABLE 1e.—*The Effect of Graded Resection on the Mean Twenty-Four-Hour Daily HCl Secretion from the Innervated Fundic Pouch in D-648*

	Fundic Mucosa Present		HCl Secretion		
	Wt., Gm.	% of Total	mEq.	% of Control	Samples, No.
Total fundic pouch	69.6	100	23.0	100	40
Fundic resection I	40.6	58.4	17.0	74	48
Fundic resection II	26.6	38.2	14.0	61	29
Fundic resection III	9.0	12.9	0.3	1.3	48

TABLE 1f.—*The Effect of Graded Resection on the Mean Twenty-Four-Hour Daily HCl Secretion from the Innervated Fundic Pouch in D-650*

	Fundic Mucosa Present		HCl Secretion		
	Wt., Gm.	% of Total	mEq.	% of Control	Samples, No.
Total fundic pouch	58.5	100	32.0	100	47
Fundic resection I	33.0	56.5	21.0	65.7	38
Fundic resection II	18.5	31.6	4.7	14.7	35

the stomach produces a rather consistent decrease in secretion after each operation. There is a reasonably close correlation between the per cent of total mucosa remaining and the per cent of control secretion

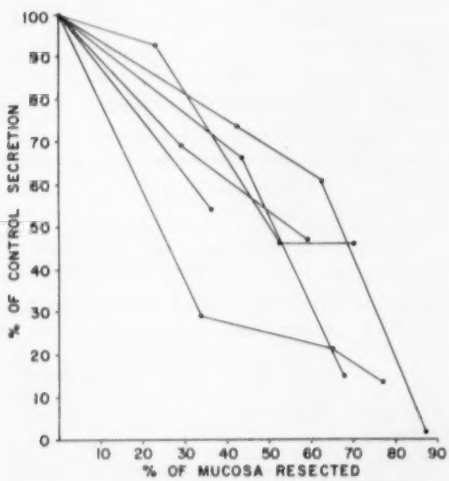

Fig. 2.—Effect of graded resection of an innervated fundic pouch on the mean 24-hour daily secretion.

(Fig. 2). In D-647, however, the fall-off in secretion was more rapid than the amount of musoca resected, while in D-647 the secretion remained high until the final resection.

The secretory data are expressed only in milliequivalents for the sake of simplicity. It is interesting to note, however, that the decrease in total quantity of acid is influenced initially mainly by a drop in the volume, whereas a significant decrease in the free acid concentration occurs only in the later stages of resection.

Part II. The Effect of Graded Resection of an Innervated Fundic Pouch on the Secretory Response to a Quantitative Insulin Test.—The gastric secretory response to insulin hypoglycemia has long been used as the indicator of an intact vagal pathway from the brain to the stomach. Standardization of the stimulus and collection period suggested that this should be a quantitative test which could be compared after each operation. Accordingly, a dose of 10 units of regular insulin was given intravenously and the secretions were collected for 100 minutes.[4] The dogs were fasted for 24 hours prior to testing, and frequently the control secretions had little or no free acid.

These data might be expected to throw a somewhat more specific light on the problem of duodenal ulcer than the 24-hour collections, because the insulin test may be considered a measure of the maximum available vagal stimulus for the 100-minute period.

Data are available on five dogs (Tables

TABLE 2a.—*The Effect of Graded Resection of an Innervated Fundic Pouch on the Secretory Response to a Quantitative Insulin Test in D-315*

	% of Total Fundic Mucosa Present	HCl Secretion in 100 Min.		Tests, No.
		mEq.	% of Control	
Total fundic pouch	100	5.0	100	1
Fundic resection I	76.5	----	----	----
Fundic resection II	47.8	3.1	62	1
Fundic resection III	29.6	1.8	36	2

TABLE 2b.—*The Effect of Graded Resection of an Innervated Fundic Pouch on the Secretory Response to a Quantitative Insulin Test in D-626*

	% of Total Fundic Mucosa Present	HCl Secretion in 100 Min.		Tests, No.
		mEq.	% of Control	
Total fundic pouch	100	6.4	100	2
Fundic resection I	64.3	3.7	58	2

TABLE 2c.—*The Effect of Graded Resection of an Innervated Fundic Pouch on the Secretory Response to a Quantitative Insulin Test in D-647*

	% of Total Fundic Mucosa Present	HCl Secretion in 100 Min.		Tests, No.
		mEq.	% of Control	
Total fundic pouch	100	2.0	100	2
Fundic resection I	67	1.4	70	3
Fundic resection II	34.6	0.3	15	2
Fundic resection III	23.2	0.3	15	2

TABLE 2d.—*The Effect of Graded Resection of an Innervated Fundic Pouch on the Secretory Response to a Quantitative Insulin Test in D-648*

	% of Total Fundic Mucosa Present	HCl Secretion in 100 Min.		Tests, No.
		mEq.	% of Control	
Total fundic pouch	100	3.0	100	2
Fundic resection I	58.4	0.6	20	2
Fundic resection II	38.2	0.6	20	2
Fundic resection III	12.9	0	0	1

TABLE 2e.—*The Effect of Graded Resection of an Innervated Fundic Pouch on the Secretory Response to a Quantitative Insulin Test in D-650*

	% of Total Fundic Mucosa Present	HCl Secretion in 100 Min.		Tests, No.
		mEq.	% of Control	
Total fundic pouch	100	2.2	100	2
Fundic resection I	56.5	0.7	31.8	2
Fundic resection II	31.6	0.2	9.1	2

2a to 2e).* The data from four of the five dogs indicate that the quantitative response to insulin stimulation falls off somewhat more rapidly percentagewise than the amount of mucosa removed. In the other dog the secretions correlate closely with the amount of mucosa (Fig. 3).

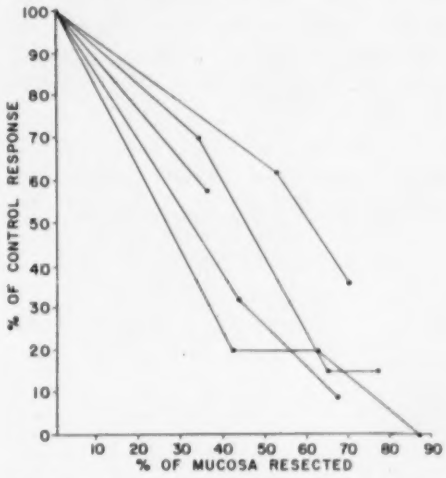

Fig. 3.—Effect of graded resection of an innervated fundic pouch on the response to a quantitative insulin test.

Again, for the sake of simplicity, the data are presented only in milliequivalents. It is interesting to note, however, that again the main effect of the graded resections on the response to insulin was to decrease the volume; the free acid concentration changed only slightly until the final stages of resection.

Part III. The Effect of Graded Resection of an Innervated Fundic Gastric Pouch on the Secretory Response to a Quantitative Histamine Test.—Histamine is the most consistent and potent stimulus of the acid-secreting cells. Here, again, standardization of the stimulus and collection period in each dog created another possible method of evaluating quantitatively the secretory

* The insulin tests of the sixth dog were qualitatively positive, thus assuring good innervation to the pouch, but unfortunately the dosage schedule was variable and, therefore, quantitative comparisons cannot be made.

ability of the pouch after each resection. In one dog 0.2 mg. of histamine base was injected subcutaneously, and in the other four dogs 1.0 mg. was used. The juice was collected for 120 minutes, and the results are expressed in milliequivalents and in percent of the control response. These responses were assumed to measure the maximum secretory effort ("secretory mass") of the pouch that is independent of the vagi.

TABLE 3a.—*The Effect of Graded Resection of an Innervated Fundic Pouch on the Secretory Response to a Quantitative Histamine Test in D-425*

	% of Total Fundic Mucosa Present	HCl Secretion in 120 Min.*		Tests, No.
		mEq.	% of Control	
Total fundic pouch	100	5.0	100	1
Fundic resection I	70.7	3.15	63	2
Fundic resection II	41.2	1.51	30.2	2

*Response to 0.2 mg. histamine.

TABLE 3b.—*The Effect of Graded Resection of an Innervated Fundic Pouch on the Secretory Response to a Quantitative Histamine Test in D-626*

	% of Total Fundic Mucosa Present	HCl Secretion in 120 Min.*		Tests, No.
		mEq.	% of Control	
Total fundic pouch	100	41.0	100	1
Fundic resection I	64.3	13.1	32	2

*Response to 1.0 mg. histamine.

TABLE 3c.—*The Effect of Graded Resection of an Innervated Fundic Pouch on the Secretory Response to a Quantitative Histamine Test in D-647*

	% of Total Fundic Mucosa Present	HCl Secretion in 120 Min.*		Tests, No.
		mEq.	% of Control	
Total fundic pouch	100	26.8	100	1
Fundic resection I	67	6.3	23.5	2
Fundic resection II	34.6	4.7	17.5	2
Fundic resection III	23.2	2.5	9.3	2

*Response to 1.0 mg. histamine.

TABLE 3d.—*The Effect of Graded Resection of an Innervated Fundic Pouch on the Secretory Response to a Quantitative Histamine Test in D-648*

	% of Total Fundic Mucosa Present	HCl Secretion in 120 Min.*		Tests, No.
		mEq.	% of Control	
Total fundic pouch	100	18.6	100	1
Fundic resection I	58.4	8.0	43	2
Fundic resection II	38.2	5.2	28	2
Fundic resection III	12.9	0.45	2.4	2

*Response to 1.0 mg. histamine.

TABLE 3e.—*The Effect of Graded Resection of an Innervated Fundic Pouch on the Secretory Response to a Quantitative Histamine Test in D-648*

	% of Total Fundic Mucosa Present	HCl Secretion in 120 Min.*		Tests, No.
		mEq.	% of Control	
Total fundic pouch	100	13.3	100	1
Fundic resection I	56.5	5.5	41.3	4
Fundic resection II	31.6	2.3	17.3	2

*Response to 1.0 mg. histamine.

The data from all five of the dogs (Tables 3a to 3e) indicate that the quantitative response to histamine stimulation falls off much more rapidly percentagewise than the amount of mucosa removed (Fig. 4).

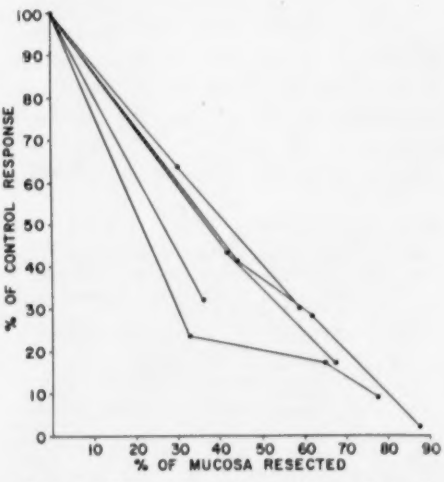

Fig. 4.—Effect of graded resection of an innervated fundic pouch on the response to a quantitative histamine test.

Again, the drop in acid production with resection was due to a decrease in volume and there was very little change in acid concentration until the final resections.

Comment

These experiments indicate that an almost direct relationship does exist between the amount of mucosa present and the secretion measured in the 24-hour daily collections (Fig. 2). The data concerning insulin and histamine stimulation show that the responses to each decreased more rapidly percentagewise than the amount of mucosa removed (Figs. 3 and 4). A representative experiment comparing all three methods of study is summarized in Figure 5.

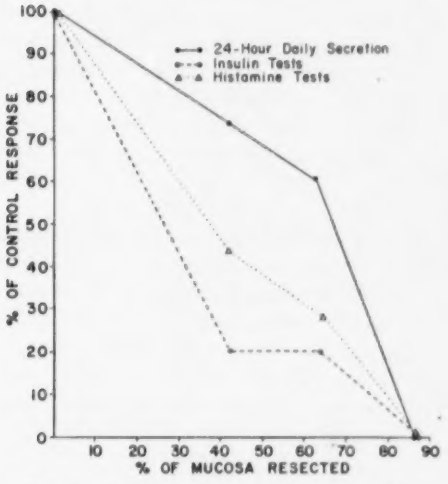

Fig. 5.—Correlation of the effect of graded resection of an innervated fundic pouch on the mean 24-hour daily secretion and the response to quantitative insulin and histamine tests in D-648.

The ability of the vagus nerves to stimulate hypersecretion is clearly limited by the amount of fundic mucosa available to respond. Since great care was taken at the time of operation not to damage the vagi and since definite responses to insulin were obtained, it must be assumed that, in spite of the standard strong stimulus, the diminished response to insulin was due to a diminished number of end-organs. Similarly, the data of the 24-hour daily secretions show a decline proportional to the amount of mucosa resected and, presumably, the animal was exposed to the same number of psychic stimuli. Thus, in spite of intact vagi, a given number of nervous impulses will not hyperstimulate the smaller amount of mucosa and call forth the same response as from the original pouch.

The consistent observation that the change in acid output was a reflection of the decrease in volume until the final stages of resection indicates that there are relatively less acid-secreting cells at the apex of the fundus. These findings confirm the histologic studies that have reported fewer parietal cells near the cardia of the stomach and would militate against very high gastric resections for peptic ulcer.

Summary

The secretory characteristics of total innervated fundic pouches of the stomach were studied quantitatively by three methods: the 24-hour collections, the response to a standard insulin test, and the response to a standard histamine test.

The pouches were resected in three stages, with the nerve supply kept intact, and were studied after each operation.

An almost direct relationship was found to exist between the amount of fundic mucosa present and the 24-hour daily gastric secretions. The gastric secretory response to insulin and histamine fell off much more rapidly.

The free acid concentration did not fall significantly until the final stages of resection, which suggests that the cardiac end of the stomach is poor in acid-secreting parietal cells.

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Symptomatic Blind Segment of Intestine Following Side-to-Side Anastomosis of Intestine

Review of the Literature and Report of a Case

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Although probably most surgeons prefer to establish continuity of the intestinal tract by end-to-end anastomosis after resection or division of the bowel, still a considerable number of surgeons continue to establish side-to-side anastomoses. In addition to the usual complications which may follow end-to-end anastomoses, side-to-side anastomoses may produce a series of complications if the proximal segment of the bowel distal to the anastomosis is excessive. Dilatation and hypertrophy of this segment may develop, resulting in a gradually enlarging pouch which may progress to ulceration and perforation.

As early as 1906 Cannon and Murphy [1] observed, in cats, that the proximal segment of a side-to-side anastomosis failed to empty properly if a redundant segment were left beyond the site of anastomosis. Estes and Holm,[2] in 1932, and Pearce,[3] in 1937, using dogs, demonstrated that when peristalsis was towards the blind proximal segments of bowel distal to a side-to-side anastomosis, when established either between the ileum and colon or between segments of the small bowel, the blind segments became dilated, hypertrophied, and filled with inspissated intestinal content, resulting frequently in perforation. If perforation did not occur, anorexia, lethargy, emaciation, and finally death ensued after three or four weeks. When peristalsis was away from the blind segment, functionless segments of bowel resulted.

Relatively few reports of clinical cases appear in the literature. Most probably, in most instances, few symptoms arise from these redundant segments, as the length of bowel left distal to the anastomosis usually is not excessive. Ashton and Baldy,[4] in 1891, and Küttner,[5] in 1896, recognized dilatation and hypertrophy of the proximal blind segment of bowel following side-to-side anastomosis with division of the bowel. Rankin, Bargen, and Buie [6] noted, at necropsy, slightly dilated blind segments of ileum many years after resection. Pickhardt [7] reported a case of side-to-side ileotransversecolostomy with division of the bowel, in which a dilated segment formed distal to the anastomosis but resulted in no symptoms.

Several cases in which serious symptoms were produced by redundant loops have been reported in the literature. Turner [8] reported a case in which the dilated pouch perforated when the patient fell down stairs. Sletten, in discussing Pickhardt's [7] paper, also described a case in which perforation occurred. Estes and Holm [2] reported a similar case. Ginzburg, Colp, and Sussman,[10] in 1939, reported three symptomatic cases after the performance of side-to-side ileocolostomy with division of the bowel. Black and McEachern,[11] in 1948, reported five such cases—three cases in which the anastomosis was between the ileum and the colon and two cases in which the anastomosis was between segments of small bowel. Clawson,[12] in 1953, presented a case and mentioned three more cases after his article had been submitted for publication.

A review of the previously reported cases reveals that the complaints in order of fre-

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quency are crampy abdominal pain, fatigue, nausea, distention or the presence of a palpable mass, episodes of diarrhea, weakness, inability to gain weight, and anemia.

The paucity of cases in the literature prompted us to report the following case.

Report of Case

A Negro boy aged 7 years was admitted on Sept. 4, 1948, to the Methodist Hospital in Fort Wayne, Ind., because of crampy abdominal pain, vomiting, anorexia, abdominal distention, anemia, underdevelopment, and general malnutrition. These symptoms had appeared approximately one year prior to admission and had become more pronounced during the previous year.

Two years prior to this admission, following resection of a gangrenous ileocolic intussusception, elsewhere, a side-to-side anastomosis had been established, between the cecum and terminal ileum. An excessive length of proximal ileum had been left distal to the anastomotic site.

The patient had been previously admitted by his family physician to the Methodist Hospital, Fort Wayne, Ind., on May 29, 1948, because of crampy abdominal pain, anorexia, failure to gain weight, and marked anemia. At that time three transfusions were given. He was dismissed June 5, 1948, considerably improved.

Physical examination on admission disclosed a pale underdeveloped Negro child with a markedly distended abdomen. The blood pressure was found to be 100 mm. of mercury systolic and 80 mm. diastolic. The heart and lungs were normal. A smooth slightly tender mass was palpated in the right lower quadrant of the abdomen. Peristalsis was active and visible. The leukocytes numbered 5600 per cubic millimeter of blood. The value for hemoglobin was found to be 10.4 gm. per cubic centimeter of blood. The urinalysis was negative. Roentgenographic examination of the chest and stomach gave negative results, and examination of the colon revealed a normally functioning stoma between the ileum and the cecum and the presence of a dilated blind segment of small bowel. It was our clinical impression that the patient's symptoms were due to a dilated blind loop of intestine.

Laparotomy was performed on Sept. 18, 1948, through a right lower rectus incision. A functioning side-to-side anastomosis between the terminal ileum and cecum was found. Distal to the side-to-side anastomosis there was a huge dilated pouch formed by the enlarged proximal segment of ileum, approximately 20 cm. long and 10 cm. in diameter (Fig.). The anastomosis was taken down, the dilated pouch of ileum was resected, and a new end-to-side anastomosis was established between the proximal ileum and the cecum. An incidental appendectomy was also performed. The child made an uneventful recovery and was dismissed from the hospital on Sept. 28, 1948, ten days after surgery.

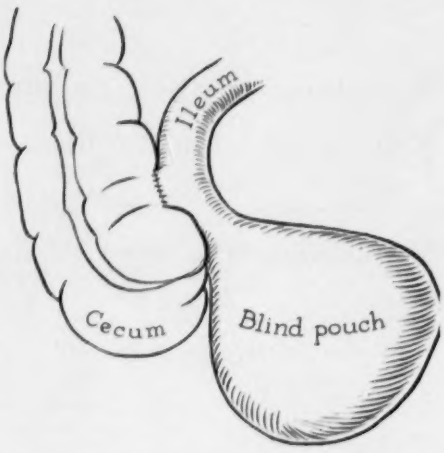

Diagram of the redundant dilated blind loop of small bowel distal to the side-to-side anastomosis.

Since that time the child has developed normally and has remained well.

Comment

Review of the cases reported in the literature as well as the case reported here indicates that potential hazards are inherent in the establishment of side-to-side anastomoses after division or resection of the bowel.

Experimentally, it has been demonstrated that long segments of proximal bowel must be left distal to the side-to-side anastomosis to produce dilated, hypertrophied pouches.

The classical symptoms of anorexia, nausea, borborygmus, crampy abdominal pain, and anemia were present in the case reported. Why anemia develops in some cases and not in others is a matter of conjecture. Cameron, Watson, and Witts,[13] who have reviewed this interesting phase of the entity, have attributed its presence to the absorption of toxic products.

Although the development of pathologic blind pouches is not frequent, construction of the stoma as near as possible to the

distal end of the proximal segment will further reduce the incidence of this hazard.

In view of the potential hazards associated with side-to-side anastomoses, it is evident that end-to-end anastomoses are ordinarily preferable to the former.

Summary

A case is reported in which a dilated, hypertrophied blind segment of bowel developed after side-to-side anastomosis following intestinal resection when continuity was established.

A brief review of history, symptomatology, pathology, and treatment is reported.

The superiority of an end-to-end anastomosis over a side-to-side anastomosis is suggested.

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Esophageal Hiatus Hernia

A Problem in Surgical Physiology

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Since about 2% of patients with symptoms warranting an x-ray gastrointestinal study are shown to have some degree of esophageal hernia, it can be assumed safely that the condition is relatively common. Since so few patients come to surgery for this condition, it can be assumed further that esophageal hernia usually is not symptomatic or can be managed by a medical regimen. With these two points in mind it becomes clear that the surgeon must be fairly certain that the patient will be benefited by the operation before it is undertaken. The "nervous" patient is not a candidate for operation unless the condition is severe and accompanied by demonstrable structural changes, such as esophagitis, hemorrhage, volvulus of the stomach, esophageal ulcer, or stricture. The patient with multiple complaints is not a good candidate unless it can be clearly pointed out to the patient just which symptoms are apt to be alleviated. The patient should accept the concept that the local condition can be corrected but that all the various personal inadequacies and their manifestations are outside the sphere of surgical attack. In other words, the surgeon must realize that if he operates upon patients who complain of a common condition which rarely causes other patients difficulty he will accumulate a large operative experience but will have a large number of poor results in dissatisfied patients. On the other hand, we operated upon a man who left the service because of "psychoneurosis, severe" and had three years of electroshock therapy. He had high gastric acidity, peptic esophagitis, and ulceration with hiatus hernia, and his operative result was satisfactory to us and to him. There is one other group of patients in whom esophageal hiatus hernia should not be repaired. It has been shown that pregnant women frequently show small hiatus herniations, and there is a definite correlation between the number of pregnancies and the incidence of hernia. For example, 18% of multiparous pregnant women showed some degree of hiatus hernia, whereas only 5% of women pregnant for the first time showed such a defect. Furthermore, of positive cases examined after delivery, only a third still showed a hiatus hernia which could be demonstrated on x-ray examination.[1] Here again, definite structural changes should be present before operation is indicated.

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Types of Esophageal Hiatus Hernia

Herniation of abdominal contents into the pleural cavity may occur through the esophageal hiatus or through congenital defects in the diaphragm: the foramen of Bochdalek (a normal pleuroperitoneal opening in the

Fig. 1.—This large, 16-cm. hiatal-type hernia was seen in a 60-year-old obese white man, it having been known to be present for 11 years with minimal esophagitis, progressive dysphagia, vomiting, and substernal pain for the past year. This film was taken in Tredelenburg position. The hernia was repaired on Sept. 15, 1954.

Fig. 2.—This large parahiatal type recurrence developed on the seventh postoperative day following severe retching after removal of the nasogastric tube. The cardia remains below the diaphragm and the original hernia repair is intact.

costovertebral region of the fetus) or the foramen of Morgagni anteriorly. It is important to distinguish these from eventrations of the diaphragm, where the abdominal organs, though located within the thoracic cage, are nonetheless separated from the pleural cavity by the weakened and thinned muscle and fibrous tissue of the diaphragm. At least 97% of the diaphragmatic hernias occur at the esophageal hiatus.[2]

Two principal types of herniation through the esophageal hiatus may be distinguished: the sliding type and the paraesophageal or parahiatal type; a combination of these two types is sometimes seen. The sliding or "short esophagus" type is found in more than 90% of cases.[3] It includes those cases formerly classified as normal esophagus with pulsion-type hernia. The cardiac end of the stomach rises into the chest, and the esophagus is shortened by muscular contraction, or in some cases, submucosal fibrosis. The paraesophageal or parahiatal hernia is characterized by an esophagus of normal length with the cardia of the stomach in the abdomen, but the anterior wall and later the greater curvature of the stomach roll upward into the hernial sac so that in advanced cases the stomach lies upside down in the chest. The gastrocolic ligament may pull the transverse colon into the chest as well. This hernia is beside and not through the hiatus. The congenitally short esophagus with thoracic stomach is said to result from failure of the stomach to descend properly and closure of the developing diaphragm about it. The portion of the stomach in the chest does not greatly exceed the diameter of the esophagus, and may not be distinguishable radiographically, but can be readily identified at operation.[4] Most cases of sliding hiatus hernia with short esophagus were formerly classified in this group, but recognition of the role of reflux esophagitis in the production of submucosal fibrosis and shortening of the esophagus has led to the belief that the congenitally short esophagus is rare.[5] A combination of sliding and paraesophageal types is sometimes seen and it is

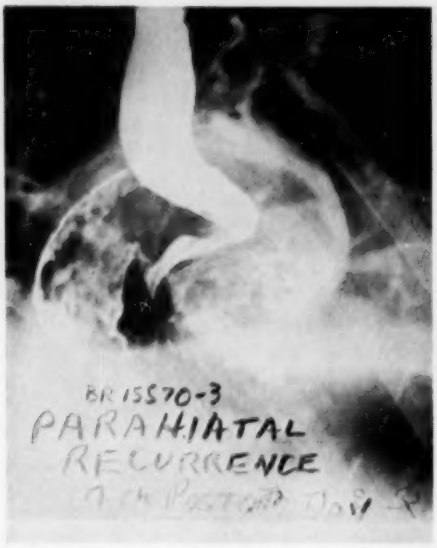

Fig. 3.—The rent in the left leaf of the diaphragm is shown with the large herniated fundic pouch. The patient refused reoperation at this time and left the hospital on the 14th postoperative day.

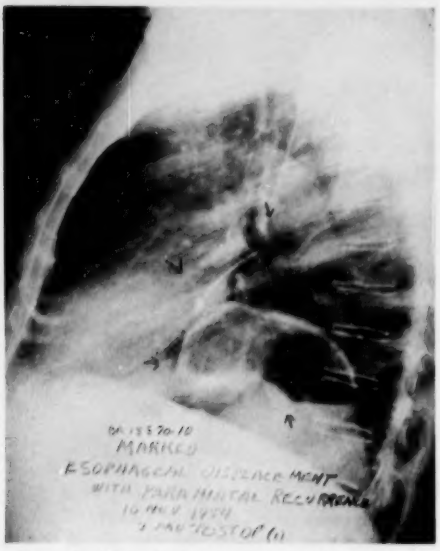

Fig. 4.—The patient was readmitted nine weeks postoperatively with inability to swallow food or liquids due to torsion of the herniated fundic pouch on the esophagogastric junction as an axis. A transthoracic reduction of the 12 cm. pouch was done with two-layer imbrication of the lateral diaphragmatic defect on Nov. 24, 1954. The primary posterior repair was found to be solidly intact, with the esophagogastric junction remaining below the diaphragm.

important that the surgeon be aware that two defects must be repaired.

Etiology

Delayed descent of the stomach and closure of the diaphragm about the cardiac portion of the stomach rather than the esophagus is said to be the fundamental cause of all hernias at the esophageal hiatus.[6] Subsequent descent of the stomach leaves an enlarged hiatus esophagus through which peritoneum and stomach may protrude when the intra-abdominal pressure increases. Hiatus hernia was the second most frequent defect found in the roentgenological examination of 3448 patients with symptoms referable to the upper gastrointestinal tract. Duodenal ulcer was found in 705 cases and hiatus hernia in 308, or 9%, of the cases; 1.3% of patients without symptoms were found to have a hiatus hernia.[7] Symptomatic hiatus hernia may occur at any age, but the great majority of patients present themselves in the 40- to 70-year-old group. Obesity is present in one-half of the cases. Pregnancy, trauma, and weight loss may each play a part. Vagus nerve stimulation in dogs may cause shortening of the esophagus, and it is possible that long-continued vagal stimulation either from central or reflex causes might play a part in pulling the stomach into the chest. Shortening of the esophagus due to scleroderma may produce a sliding-type hiatus hernia.[6,8] Since the symptomatology and sequelae of the two types differ, it is important for the physician to accurately distinguish the type of hernia.

Anatomy

The esophagus normally passes through the diaphragm and makes a bend to the left, entering the stomach obliquely. Four factors serve to prevent regurgitation of stomach contents into the esophagus: (1) the cardiac sphincter of the stomach, (2) the valve-like flap of gastric mucosa produced by the oblique junction of the esophagus with the stomach, (3) angulation of the terminal

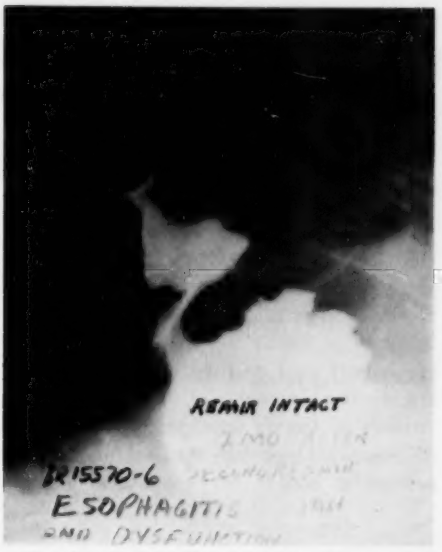

Fig. 5.—A follow-up examination two months after the parahiatal repair reveals both repairs to be intact. Superficial esophagitis was noted on esophagoscopy, but this responded to medical management. Eighteen months later the patient had some slight occasional dysphagia, postural regurgitation, and postprandial discomfort relieved on self-medication.

esophagus, produced by a sling of muscle fibers from the right crus of the diaphragm, and (4) compression of the esophagus as it passes through the diaphragm. There may also be a functional sphincter of the terminal esophagus at the point of attachment of the phrenoesophageal ligament.

As the esophagus passes through the diaphragm, it is well supported laterally by strong pillars of muscle from the right crus of the diaphragm which unite in front of the esophagus. Posteriorly, these fibers attach to the lumbar spine, but the defect behind the esophagus is rather weakly closed by fibers from the left crus of the diaphragm. Pressure within the hiatus will then be most apt to split the muscle fibers posteriorly.[9] The cardia is normally held in place by ligamentous attachments and by muscular action. The deep fascia of the undersurface of the diaphragm is continued up through the hiatus and becomes continuous with the fascia propria of the esophagus, forming the phrenoesophageal ligament. The peritoneal covering of the stomach is reflected onto the undersurface of the diaphragm. Between this layer of peritoneum and the phrenoesophageal ligament are blood vessels, lymph nodes, and some areolar tissue. It may be that loss of fat from this region is a factor in the subsequent development of hiatal hernia. Weakness of the supporting tissues about the hiatus will allow the cardiac end of the stomach to be pushed up through the aperture into the chest, forming a sliding type of hernia. The hernial sac is formed anteriorly of peritoneum, posteriorly of stomach. The esophagus shortens by elastic recoil, and the thoracic portion of the stomach hangs at its lower end like a bell. Only the intrinsic cardiac sphincter remains to prevent reflux of gastric juice into the lower esophagus. The symptoms of this type hernia are predominantly those which result from incompetence of the cardia: belching, substernal pain, heartburn, regurgitation, and dysphagia.

The paraesophageal hernia is not truly a hiatus hernia. The ring of diaphragmatic muscle about the esophagus is preserved, even though it may be represented in one area by a few fibers only.[4] Since the cardia of the stomach is fixed below the diaphragm, herniation occurs by the anterior wall of the stomach rolling upward through the defect into the hernial sac of peritoneum. As more stomach enters the sac, the greater curvature comes to lie uppermost and the pylorus and cardia are brought close together. The gastrocolic omentum may cause the transverse colon to follow the stomach into the chest. The symptoms of parahiatal hernia are usually due to the presence of a mass in the chest between the pericardium and the spine: fullness after meals, pressure in the chest, shortness of breath, pain radiating to left shoulder and down the arm, sometimes anemia from constant small losses of blood. Gastric reflux does not occur. Volvulus with obstruction is unusual.

Symptoms

A large proportion of persons with hiatus hernia have no symptoms, the defect being

discovered in the course of examination for other causes. Many patients have symptoms which differ very little from those of duodenal ulcer or functional gastrointestinal diseases. The dyspepsia associated with gallbladder disease may sometimes be ascribed to a coexistent hiatus hernia.

Symptoms due to the presence of stomach in the chest: epigastric or substernal pain following meals and associated with distention, fullness, "wind around the heart," particularly if aggravated by reclining or lifting and relieved by assuming the erect position or walking about, will suggest the possibility of hiatus hernia. The distress often awakens the patient at night and may be present upon awakening in the morning. Vomiting and intermittent dysphagia are frequent symptoms. Shortness of breath and precordial distress are present in about 25% of symptomatic cases; radiation to the left shoulder and down the left arm occurs in 10% and may lead to an erroneous diagnosis of angina pectoris. If the history relates the symptoms to the recumbent position or to exertion, particularly those forms which increase intra-abdominal pressure, such as lifting or bending forward, it is strongly suggestive of hiatus hernia, but such correlation is often absent.

Symptoms due to interference with the mechanism of the cardia: They occur only in cases of sliding hernias. Pain or distress is the most frequent complaint (75%). It is described as "sour belching," "acid regurgitation," or heartburn, although a few patients will characterize the sensation as substernal pain and may describe radiation to the back, shoulders, or left arm. Obstruction to swallowing is a common complaint (75%)[6] in a series of patients treated surgically; 8%-16% in medically treated series.[2,10] This will obviously vary with the severity of the esophagitis and the degree of esophageal spasm and stricturing which may be present. Regurgitation, nausea, and vomiting occur intermittently; undigested food may be brought up. Belching is an almost constant finding; it often affords some measure of relief. Hematemesis or melena occurs in about 8% of symptomatic cases and may be severe enough to threaten life. Usually the bleeding proceeds rather slowly, producing a moderate hypochromic microcytic anemia.

Diagnosis

The history of epigastric fullness, substernal distress, "gas," and belching, particularly if aggravated by reclining and relieved by the erect position, will suggest the possibility of a hiatus hernia. Dysphagia and esophageal pain will direct the physician's attention to examination of the esophagus. Attacks of angina on effort, in the absence of other evidence of cardiac disease, will prompt a search for esophageal disease. Usually the physical examination is unrevealing, but some tenderness or moderate muscle guarding may be found in the uppermost portion of the epigastrium.

Roentgenologic examination is the essential diagnostic study. The radiologist is asked to determine (1) the presence and type of hernia, (2) reducibility, (3) abnormalities of the esophagus: shortening, stricture, ulceration, dilatation, functional spasm. The demonstration of a hiatus hernia is best accomplished with the patient prone and in the Trendelenburg position. Careful fluoroscopic observation must be made early in the examination to distinguish the course of the barium in paraesophageal hernias. When the stomach has been filled with barium, various maneuvers are conducted in an effort to force the stomach through the hiatus. Large hernias are readily apparent, but repeated examinations may be required for the demonstration of certain small hernias. The presence of a portion of the stomach above the diaphragm establishes the diagnosis; shadows of gastric rugae differentiate the bulge just above the diaphragm from the bulge of a phrenic ampulla.

Esophagoscopy and gastroscopy are indicated in any patient with a symptomatic hiatus hernia who has evidence of hemorrhage, severe anemia, esophageal pain, dysphagia, x-ray signs of obstruction or

stricture, or for whom surgical treatment is being considered. Esophagoscopy will be of little assistance in the cases of paraesophageal hiatus hernia, but the gastroscope may occasionally show erosions or ulceration in the stomach, if the hernia is reduced at the time of the examination. Esophagoscopy permits accurate evaluation of coexisting esophagitis and ulceration, with some estimation of the severity of any esophageal obstruction in sliding hernias, but it is difficult to differentiate inflammatory narrowing of the lumen from submucosal fibrosis. Scleroderma or carcinoma of the esophagus may be detected.

Other Methods of Examination

Those patients presenting anginal complaints must obviously be thoroughly studied to exclude heart disease. This implies not only thorough physical examination and electrocardiography but also the Master's exercise test.[11] If these studies are inconclusive, balloon distention of the hiatus hernia may be attempted in an effort to reproduce the symptoms.

Medical Treatment

Medical treatment will prove satisfactory in almost all cases of uncomplicated esophageal hiatus hernia. Proper management is given for other coexisting diseases, and an effort is made to give the patient insight into any emotional problems which may be present. A diet which eliminates chemically, mechanically, and thermally irritating foods is recommended, and the quantity taken at each feeding is kept small. All food and drink is forbidden for three hours before retiring; the patient is advised not to lie down during the day for one hour after eating. If night pain continues to be a problem, the head of the patients' bed may be elevated on 6-in. blocks. Antacids are helpful, particularly in the sliding hernias. Antispasmodics such as methantheline (Banthine) bromide are of doubtful value. Small doses of phenobarbital may be used for short periods of time.

Surgical treatment is reserved for those patients with complications as follows: (1) peptic esophagitis poorly controlled by medical management, (2) hemorrhage, (3) ulcer of the distal esophagus or in the herniated stomach, (4) stricture or inflammation sufficient to cause dysphagia, (5) volvulus of stomach and obstruction in the paraesophageal hernia, (6) coronary artery sclerosis when it is thought that the hiatus hernia acts as a trigger mechanism to produce angina pectoris, or if there is hemorrhage from the hernia, and (7) coexistent duodenal ulcer.

Choice of Surgical Treatment

Some poorly conceived operative treatments have been advocated as well as some needlessly radical operations. Simple crushing or excision of the left phrenic nerve is a procedure of limited applicability. This procedure does not attack the underlying causative factor and in itself is not a definitive treatment. However, in poor-risk patients with severe symptoms relaxation of the diaphragm by phrenic crush may reduce retention of acid gastric juice in the herniated stomach pouch with consequent symptomatic relief. In our experience it has given good symptomatic results and has controlled hemorrhage, but these results are temporary.

Some authors have been willing to accept the prolapsed stomach as irreparable and have simply advocated suture of the diaphragm to the stomach to prevent extension of the process.[12] This is in no way curative and certainly will have no effect on structural changes such as esophagitis, ulcer, stricture, and hemorrhage. The addition of phrenic crush or excision to this procedure is another example of the failure of addition of two poor procedures to produce one good one. Esophagogastrectomy [13] is a needlessly radical procedure, and, after excision of the lower esophagus and upper stomach, two methods of repair have been advocated. The first is esophagogastrostomy by bringing the stomach up into the chest, anastomosing the gastric pouch to the esophagus. This pro-

cedure simply succeeds in recreating a hiatus hernia, only now it is surgically instead of naturally produced. Esophagogastrostomy has the disadvantage of leaving the stomach in the mediastinum, and the patient is prone to acid esophagitis from regurgitation. The only benefit is that currently involved tissues are excised and vagotomy incident to the resection gives a temporary decrease in gastric acidity. A second type of repair is by esophagojejunostomy in Roux-Y fashion, leaving the gastric pouch with an inverted proximal end. This certainly is needlessly radical and has two distinct disadvantages. First, the patient has no gastric food reservoir and is left in the same distressing situation as the patient with total gastrectomy. Second, the empty gastric pouch has no means of neutralizing itself and experimentally we know that an acid empty stomach is more prone to ulceration. In attempting to think through the problem clearly, it seems that there are essentially three groups of patients for whom operative treatment is indicated and in each group the advocated procedure is somewhat different. The first and simplest group is composed of those patients who have a moderate-sized hiatus or paraesophageal hernia and in whom the symptoms are primarily mechanical, due to the hernia itself. These are the patients who have pain, hemorrhage and/or volvulus with a relatively normal gastric acidity and no structural changes of any degree of severity (esophagitis or ulceration). Here it seems that hernia repair alone is indicated, and the first problem is the approach. Probably there is no generally accepted answer to the question of whether adbominal or thoracic approach is preferable. This depends largely on the training and experience of the operator. The abdominal approach is more difficult because of the posterior position of the defect, and it should be remembered that division of the attachments of the left lobe of the liver allow it to be folded upon itself to permit lateral retraction. Division of the peritoneum about the hiatus allows the stomach to be pulled back into the abdomen with little difficulty usually. Now the question of repair arises. Formerly, the tendency was to push the esophagus back toward the vertebral column, decreasing the size of the hiatus by stitches placed anteriorly or anterolaterally. Allison [5] has shown that the anatomical configuration is such that the crura of the diaphragm normally leave a triangular weak area posteriorly, and Harrington [14] has shown that in 35% of patients being operated upon for other conditions one or more fingers could be inserted between the esophagus and the diaphragm. This posterior weakness explains the relatively high postoperative recurrence rate as well as the dissatisfaction of surgeons with the anterior type of repair. Allison has emphasized that the anterior margin of the hiatus always is firm and often fascial, whereas the defect is posteriorly where the crura cross and attach leaving a defect. He stresses the necessity of making the repair posteriorly, but unfortunately the situation is complicated by the fact that the hernia itself has thinned out the tissues needed for repair, and it is difficult to find good tissue posteriorly with which to repair. This is especially difficult through the anterior abdominal approach. Wangensteen [15] has advocated that the hiatus be enlarged by an anterior lateral incision through the diaphragm. The esophagus is then moved over into this new location and snug closure is made about it. This procedure has considerable merit and wide application. Some authors have advocated phrenic crushing as a temporary splint, but this is no more essential than temporary paralysis of the inguinal muscles after hernia repair. The thoracic approach seems to offer considerable advantage over the abdominal approach from the standpoint of visibility and ease of repair. The anterolateral approach, resecting the left ninth rib, gives rather poor exposure and makes the repair very difficult, partially because of the depth at which one is forced to work. The straight lateral position, resecting the left ninth rib, however, gives excellent exposure and greatly facilitates

good posterior repair. As soon as the pulmonary ligament and mediastinal pleura have been divided, the area of the hernia is readily visible. Blunt separation obviates any bleeding, and a tape can be placed about the esophagus with ease. Usually the hernia is of the sliding type, and the peritoneum is not opened. In the rarer paraesophageal type, the defect is joined with the hiatus to make one opening and the peritoneum is entered. As the dissection progresses, the vagus nerves are visualized and spared. The edges of the diaphragm are identified, and posterior repair with interrupted nonabsorbable surgical sutures is carried out, replacing all the stomach in the peritoneal cavity. This is always possible even if the diaphragm has to be elevated. The edges of the remaining hiatus then are fixed to the esophagogastric junction to prevent recurrence. This eliminates the posterior triangular defect and makes a smaller hiatus. The aorta and inferior vena cava are very close to the area of suture but offer no real problem. The mediastinal pleura is closed loosely and the chest is closed without drainage after the lung has been reexpanded.

The second group of patients is made up of those who have a moderate or large hernia, together with difficulties such as high gastric acidity, peptic esophagitis, ulceration, dysphagia, and some stricture. These patients almost always have shortening of the esophagus from inflammation, pulling the stomach up through the hiatus. Such patients have their primary difficulty with gastric acid regurgitation, and Wangensteen has written of the extreme sensitivity of the esophageal mucosa to hydrochloric acid. In such a situation, simple repair of the hernia defect will give an incomplete recovery because the acid factor still will remain a problem. In these cases the thoracic repair of the hernia as described above is combined with bilateral vagotomy to ablate the acid factor, and after closure of the thoracotomy the patient is returned to a dorsal recumbent position, and, through a short paramedian incision, a posterior short-loop gastrojejunostomy is performed to overcome the gastric retention incident to the vagotomy. It should be stated at this point that vagotomy is not advocated for duodenal ulcer, but the situation mentioned above seems to be a suitable one for vagotomy. At first glance one might think that the gastrojejunostomy could be done by incising the diaphragm, obviating the abdominal incision. However, with the patient in a lateral position diaphragmatic incision makes it very difficult to get a short loop of jejunum and the gastrojejunostomy is mechanically poorly placed. It is much preferable to employ the short abdominal incision, since the end-result is superior. These patients have the usual poor appetite, but their symptoms are relieved immediately. The third group of patients is made up of those who have a small hernia without symptoms referable to it but who have duodenal ulcer and an elevated gastric acidity. Here it seems that the duodenal ulcer is primary and the small hernia is either fortuitous or on the basis of mild acid regurgitation. In such cases, we have chosen to do a gastric resection for the duodenal ulcer, removing at least 75% of the stomach, reestablishing gastrointestinal continuity by a posterior short-loop gastrojejunostomy with a small Hofmeister-type stoma. This ablates the acid factor, and the small hernia is not significant in the absence of high acid. If the hernia is larger, it may be wise to repair the hernia also, but we have not yet found this combination of operations necessary. Thinking the problem through in this manner exemplifies a principle which we stress repeatedly. The treatment should be properly conceived to fit the needs of the patient rather than employing a routine procedure, expecting all patients to be benefited thereby.

Results of Brooke Army Hospital Series

Between December, 1952, and April, 1956, there were 21 patients who required surgical intervention for esophageal hiatus hernia and its complications. The type of procedure was planned to meet the requirements of

TABLE 1.—*Primary Procedures*

	Cases, No.
Transthoracic posterior repair of hernia—anterior advancement of esophagus	9
Hernia repair, vagotomy, gastrojejunostomy	8
Subtotal gastrectomy for duodenal ulcer; transabdominal hernia repair (1)	2
Phrenic nerve division	2
Total	21

each patient according to the previously mentioned classification as shown in Table 1.

With coordinated follow-up by the gastroenterology and surgery services it became evident that certain secondary procedures were necessary in several of these patients for specific indications. These are shown in Table 2.

TABLE 2.—*Secondary Procedures*

	Cases, No.
Transthoracic repair of recurrence: sliding type—1 (1 yr.), parahiatal—2 (2 mo.)	3
Transthoracic hernia repair + vagotomy, after gastrectomy (for stomal ulcer, high acid return)	1
Phrenic nerve division, cervical (for pinchcock action on small recurrence)	1
Subtotal gastrectomy (for esophageal stenosis and acid gastric retention)	1
Take-down nonfunctioning gastrojejunostomy (at 1 mo. — 1; at 2 yr. — 1)	2
Total	8

It should be noted that the three recurrences requiring secondary surgical repair were all precipitated during the early postoperative period; these were probably due to coughing with patchy atelectasis and to recurrent vomiting from dysfunction. Only one showed a breakdown of the posterior repair at the second procedure, allowing a large sliding-type recurrence with progressive esophagitis uncontrolled. Rather unexpected were the two parahiatal recurrences, each with an intact primary repair; in effect each had ruptured a thin portion of the left leaf of the diaphragm near the hiatus. Tremendous gastric distention within the left chest occurred in each patient, prior to secondary repair.

One patient had 75% gastric resection for duodenal ulcer, at which time it was found technically impossible to do an adequate posterior hernia repair. With a return to alcoholic and dietary indiscretions in the early postoperative period, he developed stomal ulceration and progressive reflux esophagitis; high acid return (Table 2) was demonstrated within three months for which transthoracic vagotomy and hernia repair were required.

Another patient developed a small traction-type recurrence one year postoperatively with intact primary repair; yet stasis ulceration with hematemesis from diaphragmatic pinchcock action about the fixed, elevated cardiac portion of the stomach necessitated transcervical excision of a segment of the left phrenic nerve for relief.

Of unusual interest was the patient who required secondary gastric resection for esophageal stenosis, small traction-type recurrence, and high-acid gastric retention two years after the primary procedure (Table 2). At the time of resection, numerous coils of heavy black silk, used one year previously in dilating the esophageal stenosis, were found to be producing considerable functional obstruction of the antrum, pylorus, and duodenum. With a nonfunctioning gastrojejunostomy, these coils of silk obviously contributed to the 300 cc. morning gastric retention; yet with demonstrable incompetence of the cardia, high acid return after vagotomy, and progressive esophageal stenosis it was still deemed advisable to do a 75% gastric resection according to the work of Leven and Wangensteen (1948). Incidental take-down of the nonfunctioning gastrojejunostomy was done at the time of resection, demonstrating a pseudodiverticulum formation.

One other nonfunctioning gastrojejunostomy was taken down at one month postoperatively; all subsequent anastomoses of this type were done through a small left upper paramedian incision after closure of the chest and hernia repair from above. The extremely short or no-loop posterior gastrojejunostomy functions more satisfactorily than the less-well-placed transdiaphragmatic anastomosis done at the time of hernia repair.

Follow-Up Results

With careful preoperative and postoperative management, there was no mortality in the series of 21 patients treated surgically; decreased morbidity and shorter periods of hospitalization were found to be the usual result when surgical procedures are utilized to the varying needs of each patient; these are shown in Table 3.

TABLE 3.—*Results of Surgical Therapy*

		Cases, No.
Repair only		
Degree improvement:	Excellent — 6	
	Moderate — 2	
	Slight — 1	9
Repair plus vagotomy and gastrojejunostomy		
Degree improvement:	Excellent — 4	
	Moderate — 4	8
Repair plus gastrectomy		
Degree improvement:	Moderate — 1	
	Slight — 1	2
Phrenic nerve section (poor-risk patients)		
Relief of hematemesis	— 2	2
Total		21

In consideration of the entire series without regard to the type of procedure, the follow-up results are shown in Table 4.

Individualizing the primary surgical procedures, particularly in patients having esophageal stenosis and recurrent esophagitis, has produced a rather gratifying follow-up experience. Secondary surgical procedures are felt to be an integral part of a considered program to combat the pathological physiology so distressing to these patients. Conservative, coordinated medical and surgical treatment of esophageal stenosis has been successful without radical resection in any of these patients. It is noteworthy that after early medical and surgical follow-up, for 6-12 months, most of these patients were no longer symptomatic or were able to continue medical control measures without additional hospitalization or discomfort. This type of surgical intervention, therefore, introduces no additional pathological physiology and attempts in all respects to correct the abnormal conditions secondary to esophageal hiatus hernia.

TABLE 4.—*Total Follow-Up Results*

	Cases, No.
Patients obtaining excellent improvement	10
No further treatment needed—3	
Temporary medical measures—7	
Duration follow-up: 36 mo.—4	
24-36 mo.—6	
Patients obtaining moderate improvement	7
Requiring medical only—1	
Both medical and surgical—6	
Duration follow-up: 18-36 mo.—5	
9-18 mo.—1	
2 mo.—1	
Patients obtaining slight improvement—requiring both medical and surgical management (poor patient cooperation)	2
Duration follow-up: 4-21 mo.—2	
Poor-risk patients having phrenic section	2
Requiring additional treatment—0	
Duration follow-up: Improved at discharge, 1 mo.—2	
Total	21

Summary and Conclusions

Esophageal hiatus hernia is a moderately common defect which rarely is symptomatic and more rarely still does it require surgical intervention. This means that cases must be selected for operation with considerable care.

The sliding or hiatus-type hernia makes up about 90% of the total group, and the parahiatal type is quite uncommon. In our 21 cases all were hiatal type, but there were two parahiatal type recurrences after operation. The mechanism of this is not clear.

Surgery should be reserved for those patients with large symptomatic hernia, those with severe esophagitis of recurrent type, those with esophageal ulceration, and those with residual strictures. The surgical procedure must be chosen to fit the case; therefore no "routine" treatment can be advocated. Patients can be categorized into broad groups, however, and this is discussed.

In our 21 patients eight required some secondary procedure, but in the follow-up results 10 were classed as "excellent," 7 moderately improved, and 2 slightly improved. The two patients who received phrenic section alone could be placed in the "excellent" group from the standpoint of relief of symptoms.

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Translumbar Aortography Followed by Fatal Renal Failure and Severe Hemorrhagic Diathesis

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Deaths due to diagnostic procedures are among the worst medical tragedies. They are impossible to explain to the patient's relatives and are particularly horrifying if the patient was in good health prior to the procedure. For this reason, a diagnostic procedure, to be accepted, generally, should be more than reasonably safe. Until recently, translumbar aortography seems to have fallen into this category, but the recent literature bears a disturbing number of case reports of fatal and serious complications following use of this diagnostic method (Table). We have seen a patient who died of uremia and a hemorrhagic diathesis following translumbar aortography, which prompted a review of the literature and the following case report.

Report of a Case

A 12-year-old white girl was first seen at St. Christopher's Hospital for Children in December, 1951, with chief complaints of frontal headaches and hypertension of six months' duration. On admission her blood pressure varied between 185/150 and 218/158. Physical examination and roentgen and laboratory studies revealed the following pertinent findings: Funduscopy showed generalized narrowing (Grade 3) of the retinal arterioles without retinopathy. The electrocardiogram revealed left axis deviation and evidence of myocardial strain. The size of the heart as determined by roentgenographic studies was normal. Excretory urograms employing sodium acetrizoate (Urokon sodium) revealed prompt excretion of the dye without evidence of deformity of the pelves or calyceal structures; the outline of the right kidney appeared to be somewhat smaller than that of the left. Retrograde pyelograms appeared normal, contrast medium appearing from the right (smaller) kidney before it did from the left. The specific gravity of the urine obtained from the right ureter was 1.011; that from the left was 1.008. There was 20% excretion of phenolsulphonphthalein from the left kidney in 15 minutes and 5% from the right. Urea clearances were 93% and 113%, respectively. Cold pressor and piperoxan (benzodioxan) tests were normal.

In February, 1952, the right kidney and adrenal were explored through a right subcostal incision. The right kidney appeared normal; it was 10 cm. in length. The right adrenal was not abnormal or enlarged. The left kidney was palpated transperitoneally, and it was felt that it was only slightly larger than the right. Accordingly, nephrectomy was not performed but a thoracic and lumbar sympathectomy and splanchnicectomy were done. Twelve days later a similar sympathectomy was performed on the left side. The blood pressure fell for a week after sympathectomy, but one week later it rose to its original level. However, the patient was symptomatically improved, with loss of headaches.

On March 1, 1954, the patient was readmitted to St. Christopher's Hospital for Children for reevaluation. Studies were repeated, and results of the piperoxan, tetraethylammonium chloride, and phentolamine (Regitine) tests were normal. The blood urea nitrogen level was within normal limits. Split-function studies with phenolsulphonphthalein revealed excretion of the dye from both kidneys within three minutes (normal), but the rate of flow was too slow for evaluation of kidney function. Specific gravity of the urine from each kidney was 1.005.

Because of the known disparity in the size of the kidneys, it was felt that aortography might give additional information about their blood supply and function. Accordingly, on March 15, 1954, a translumbar aortogram was performed under thiopental (pentothal) sodium anesthesia. Twenty cubic centimeters of 70% sodium acetrizoate was injected, and multiple films were made with a Sanchez Perez apparatus at approximately one-second intervals. An excellent visualization of the blood supply of both kidneys, and nephrograms

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Complications Following Aortography

Year Reported	Author & Source	Details
Renal complications		
Fatal cases		
Not mentioned	Dos Santos (cited by Colston [19])	Needle placed in front of the aortic opening of the right renal artery in a patient with a functionless left kidney; death resulted from anuria
Not mentioned	Dos Santos (cited by Colston [19])	Injection under too high pressure in a patient whose right kidney had been destroyed by tuberculosis; anuria and death followed
1954	Fry [4]	100 cc. of 70% sodium acetrizoate in 2 injections into aorta by lumbar route; death from uremia with hemorrhagic diathesis 29 days later
1954	Joselson & Kaplan [1]	15 cc. 75% sodium iodomethamate injected by translumbar route into a patient with a unilaterally atrophic kidney, normal opposite kidney; death 26 days later of uremia with hemorrhagic diathesis
1955	Alwall et al. [1]	2 injections of 30 cc. each of iodopyracet (Umbradil) into aorta; on one of these all the dye entered the healthy kidney; the opposite kidney was removed for tumor 3 days later; death from uremia after 37 days
1955	Alwall et al. [1]	50 cc. 70% sodium acetrizoate (Trijodyl) injected to rule out kidney tumor (negative), followed by anuria, uremia, and death after 34 days
1956	McAfee & Willson [9]	25 cc. of 70% sodium acetrizoate injected twice successively with patient recumbent and erect; film of abdomen 20 min. later showed large hematoma; death occurred from renal failure after 15 days, and autopsy showed hematoma round left kidney
1956	Conger et al.	20 cc. 70% sodium acetrizoate injected into aorta of child with atrophy of one kidney, normal opposite kidney; death occurred from uremia with hemorrhagic diathesis 12 days later
	Total, 8 deaths	
Nonfatal cases		
Not mentioned	Root (cited by McAfee & Willson [9])	Temporary renal shutdown secondary to embolic obstruction of the aorta following 3 injections of 20 cc. of 70% sodium acetrizoate; recovery after peritoneal lavage and use of artificial kidney
1952	LeRiche (cited by McAfee & Willson [9])	Temporary oliguria and vomiting
1953	Harvard [6]	Hematuria after injection of contrast medium into one renal artery
1954	Miller et al. (7 cases) [16]	4 cases of bilateral injury as demonstrated by the oliguria-uremia syndrome; 3 cases of unilateral injury secondary to injection of all of the contrast medium into one kidney
1956	Olsson (cited by Colston [19]) (9 cases)	N.P.N. elevation followed aortography
1956	McAfee & Willson [9]	Direct injection of 70% sodium acetrizoate into the right renal artery resulting in death of the kidney by interstitial fibrosis and nephrectomy 9 wk. later
1956	Ramey & Polley (cited by McAfee & Willson [9])	15 cc. of 70% sodium acetrizoate injected into aorta at the origin of the right renal artery with intense opacification of the right kidney; this was followed by atrophy and poor function of that kidney
	Total, 21 cases	
Extrarenal complications		
Fatal cases		
1950	Wagner & Price [18]	Gangrene of the bowel following injection of the superior meseneteric artery with sodium iodide
Not reported	Dos Santos (cited by Colston [19])	Gangrene of the bowel following interstitial extravasation at the level of origin of the inferior mesenteric artery
Not reported	Dos Santos (cited by Colston [19])	Rupture of the aorta following intra-adventitial injection
1956	Baurys [2]	Death following paraplegia secondary to translumbar aortography
Nonfatal cases		
1950	Nelson (2 cases) (cited by Baurys [2])	Paraplegia following translumbar aortography
1953	Abeshouse (cited by Baurys [2])	Paraplegia following translumbar aortography
1953	Maluf & McCoy [8]	Severance of thoracic duct during translumbar aortography
1954	Boyarksy [4]	Paraplegia following translumbar aortography
1954	Antoni & Lindgren (cited by Boyarsky [2])	Paraplegia following translumbar aortography
1956	Parry (cited by Baurys [2])	Paraplegia following femoral aortography

were obtained (Fig. 1*A*). However, a film study 10 minutes later showed no visualization of the acetrizoate within the renal pelves and there was a persistent nephrogram (Fig. 1*B*). On the following day there had still been no excretion of contrast medium into the collecting system of the urinary tract. Instead, the biliary tract was excreting the compound, the gallbladder being filled with radiopaque material (Fig. 1*C*). An additional 15 cc. of 30% sodium acetrizoate administered in the antecubital vein at this time failed to outline the hollow part of the urinary tract.

Course Following Aortography.—On the day following aortography the patient became ill and complained of pain and tenderness in the left flank and developed nausea and vomiting. Her blood pressure rose to 210/150. Blood urea nitrogen, determined the following morning, was 49 mg. per 100 cc., and it continued to rise gradually throughout the remainder of the hospital course, as shown in Chart 1. From this time until her death, the patient's condition showed progressive deterioration. The course was downhill, manifested by twitchings, convulsions, increasing stupor and coma, and nausea and vomiting. A hemorrhagic diathesis developed on the fifth day, with epistaxis and the passage of tarry stools. This became severer, and on the seventh day there was a terminal septicemia, with a positive blood culture of hemolytic staphylococci. As shown in the Chart, progressive oliguria developed despite adequate fluid intake, with death occurring on the 12th day after aortography.

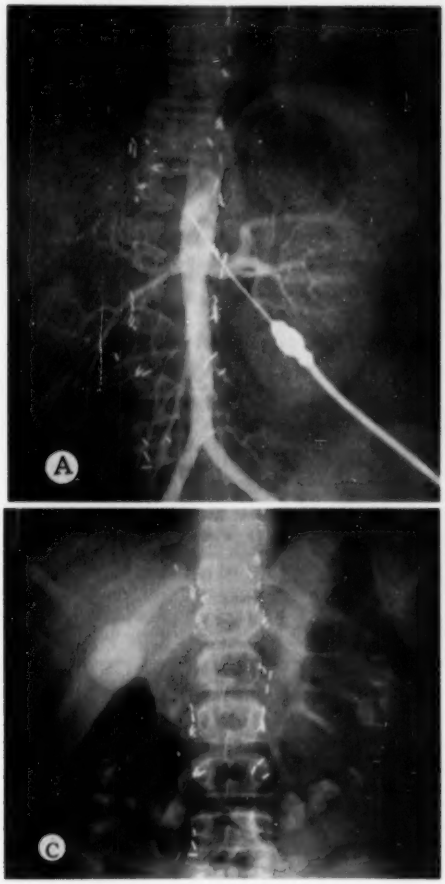


Fig. 1.—*A*, aortogram demonstrating renal arterial pattern. *B*, film exposed 10 minutes later, showing bilateral nephrograms without excretion of dye from either kidney. *C*, film exposed 18 hours after aortography, showing excretion of contrast medium through the biliary tract.

The treatment, which was ineffective, consisted of daily surveys of the blood chemistry (Chart 2); total base, chlorides, potassium, phosphates, proteins, CO_2 content, and venous pH were determined, and fluid balance was maintained, with replacement of electrolytes and fluids and corrections of the pH according to these findings. On the fifth day the first transfusion was given to replace blood loss, and from this point on estimated blood loss was replaced daily. It was felt that extracorporeal perfusion to correct the uremic syndrome was not feasible because of the bleeding diathesis. Instead, an exchange transfusion was performed on the seventh day. The only benefit resulting from this was a temporary improvement of the terminal septicemia.

Postmortem Findings.—There were multiple petechiae and eccymoses in the skin, sclerae, gastrointestinal tract, heart, and lungs. The pertinent findings were as follows: The heart was enlarged, and there was evidence of cardiac failure in the form of ascites and bilateral hydrothorax, as well as passive congestion of the abdominal organs. The left kidney weighed 365 gm.; the right, 60 gm. (Fig. 2). The orifice of the right renal artery was only slightly smaller than that of the left; there were no areas of arterial obstruction. The renal veins were free from thrombi. The left kidney was deep reddish-purple; its surface was somewhat granular, and on section the cortex and medulla were not clearly demarcated. Multiple punctate, linear and pyramidal, red to yellow zones suggesting hemorrhage were present in the left renal pelvis; neither the pelvis nor the ureter was dilated.

The central one-third of the right kidney was occupied by a smooth pale depressed scar extending from the surface to the renal pelvis. Only isolated hemorrhagic areas were present within this scar. The appearance of the remainder of the right kidney was similar to that of the left one. There was slight dilatation of the right pelvis but

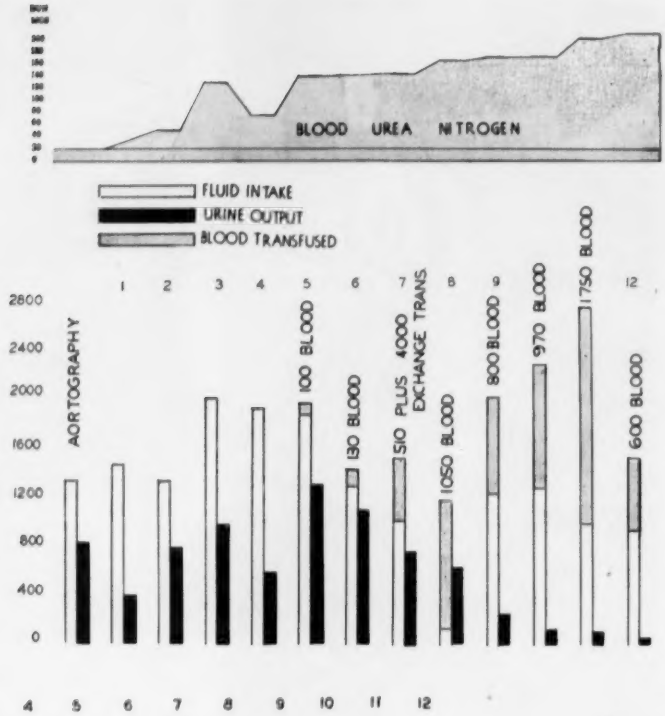
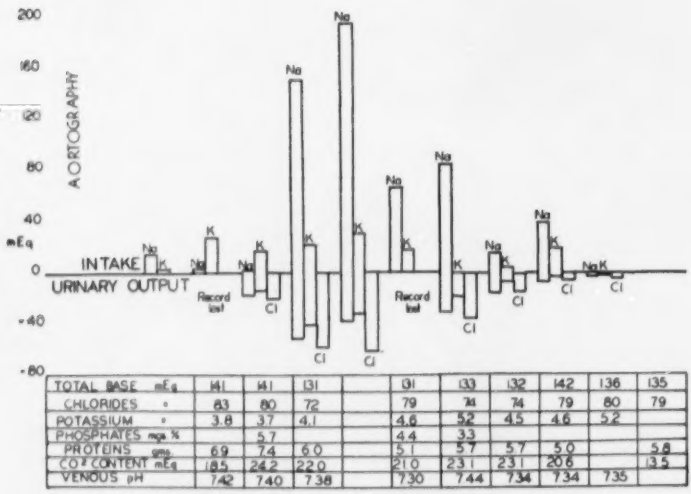


Chart 1.—Note gradually progressive oliguria and uremia despite replacement of fluids and blood.



TOTAL BASE mEq	141	141	131		131	133	132	142	136	135
CHLORIDES "	83	80	72		79	74	74	79	80	79
POTASSIUM "	3.8	3.7	4.1		4.6	5.2	4.5	4.6	5.2	
PHOSPHATES mgs %		5.7			4.4	3.3				
PROTEINS gms	6.9	7.4	6.0		5.1	5.7	5.7	5.0		5.8
CO_2 CONTENT mEq	18.5	24.2	22.0		21.0	23.1	23.1	20.6		13.5
VENOUS pH	7.42	7.40	7.38		7.30	7.44	7.34	7.34	7.35	

Chart 2. — Intake and urinary output of electrolytes as compared with plasma electrolyte values.

not of the right ureter. The mucosa of the bladder was diffusely hemorrhagic.

Histologic examination of the central one-third of the right kidney revealed almost complete disappearance of glomeruli and tubules, with a moderate infiltrate of lymphocytes (Fig. 3*B*); its appearance was more suggestive of a vascular than of an inflammatory lesion. Sections of the remainder of both kidneys revealed multiple cortical and medullary abscesses, many of which contained

Fig. 2.—Kidneys at autopsy, demonstrating disparity in size and bilateral extensive hemorrhage. The pale shrunken scar is apparent on the surface of the smaller, right kidney.

central accumulations of bacteria. There was severe interstitial hemorrhage, and abundant blood was present in the tubular lumens. The collecting tubules contained numerous acidophilic hyaline and granular casts. Patchy areas of tubular dilatation were present in addition to hyaline granular degeneration of a number of the tubular epithelial cells. In some areas the convoluted tubules were lined by a low, flattened, regenerative type of epithelium. The glomeruli were intensely engorged; a number of them were partially or completely necrotic and thrombosed (Fig. 3*A*).

Sections of the right and left renal arteries revealed reduplication of the internal elastic lamella and areas of intimal thickening. Throughout both kidneys there were necrotizing arteritis and arteriolitis in addition to elastic intimal thickening and concentric intimal proliferation of small arteries (Fig. 3*B*).

In summary, the findings were those of benign and malignant nephrosclerosis with cardiac hypertrophy and evidences of cardiac failure. Both kidneys contained extensive interstitial hemorrhage; the left kidney was almost four times its normal weight, but the right kidney was only two-thirds of its normal weight. A large depressed scar was present in the right kidney, probably as the result of vascular disease. No significant obstructive lesions were present in the major renal vessels. In addition to the interstitial renal hemorrhage there was intense engorgement of the glomeruli, with thrombosis, necrosis, and varying degrees of renal tubular degeneration. Hemorrhages were present in multiple sites in the body, and there were abscesses in the kidneys and small intestine.

Comment

This is the eighth reported case of fatal renal failure following aortography. In two of the cases reported elsewhere [3,6] and in this one there was also an associated severe hemorrhagic diathesis.

The pathogenesis of renal damage following aortography is not clear, but two factors which may have been contributory should be considered.

The first factor is the amount of contrast medium entering the kidney. In our case, and in the one reported by Joselson and Kaplan, unilateral renal hypoplasia existed, so that the better kidney received the major part of the drug. Fry's patient received three injections into the aorta, and so both kidneys received large doses. In the eight cases of renal damage reported by Alwall et al. from Sweden, five had either received repeated injections or large single amounts

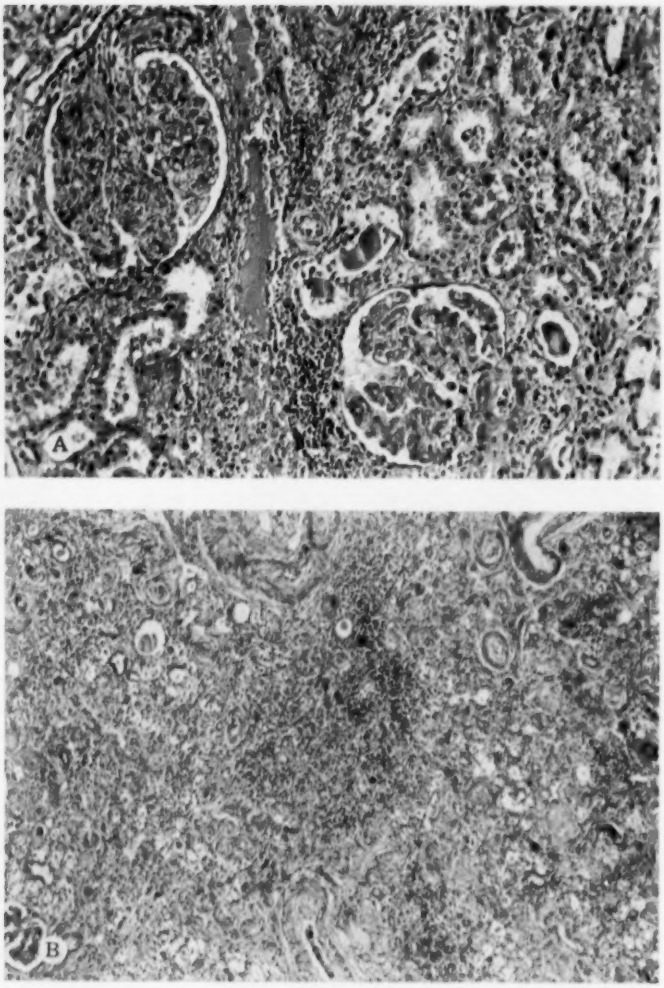


Fig. 3.—*A*, left kidney. Note the enlarged glomeruli with necrotic afferent arterioles and partial necrosis of the glomerular tufts. *B*, right kidney (atrophic one). Note the disappearance of tubules and glomeruli and concentric intimal thickening of the walls of the small arteries.

(over 50 cc.) of contrast medium into the aorta. Since high arterial concentration of iodine compounds can cause vascular spasm, such a process occurring in the kidney would delay the excretion of the compound and expose the kidney to the toxic compound for a long time. This explanation is supported by the delayed nephrogram seen in our case. The combination of high iodine concentration and prolonged arterial spasm is the probable explanation of the toxic change in the kidneys.

The second factor, namely, the possibility of sensitization to iodine compounds by previous injections of radiopaque material, must also be considered. However, this patient had undergone at least three intravenous pyelograms without evidence of sensitization on the last occasion. Furthermore, Alwall et al.[1] reported several cases of renal failure following aortography in which there was no history of preceding intravenous pyelography. In view of the many patients subjected to repeated intravenous urograms for urinary tract pathology, who show no such phenomenon, this explanation is not a probable one.

It seems likely, therefore, that large concentrations of iodine reaching the kidney through the translumbar aortic route, and remaining there for prolonged period of time owing to arterial spasm, are responsible for these cases of renal failure. The high concentrations are achieved either (1) by a single large dose or multiple repeated doses of contrast medium or (2), in patients having one good kidney with atrophy of the opposite one, by resultant increased renal circulation to the healthy kidney, resulting in its receiving an overdose of the iodine compound.

Conclusions

Nesbitt [11] has pointed out that to be of value translumbar aortography must do more than supply information; it should clinically alter or improve the management of the patient. His comment seems particularly apt in the urological field. In our experience renal angiography supplies little information of real value and is unreliable in differentiating renal cysts from tumors, the latter being a diagnostic point hailed by its advocates.

We feel that, in view of its proved nephrotoxic effect in many reported cases, renal angiography should not be used in the diagnosis of renal disease.

Summary

A death due to renal failure with hemorrhagic diathesis following translumbar aortography is reported, bringing the total of such reported cases to eight. Two other deaths from renal failure have been reported without accompanying hemorrhagic manifestations following aortography.

Translumbar aortography is dangerous from the standpoint of renal toxicity, and it should never be employed in a patient with poor renal function.

Large single doses of iodine contrast medium, or repeated small doses injected per aorta, are more nephrotoxic than a single small dose.

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Editorials

TRANSLUMBAR AORTOGRAPHY IN THE STUDY OF RENAL DISEASE

In a paper which must give pause to all advocates of translumbar aortography, Conger, Reardon, and Arey report a case of uremic death with hemorrhagic diathesis, following diagnostic translumbar aortography in a 12-year-old child with hypertension. One can certainly sympathize with their statement, "Deaths due to diagnostic procedures are among the worst medical tragedies."

They carefully review the literature and tabulate a total of eight "renal" deaths and a number of other nonfatal renal complications following this procedure. They conclude, "In view of its proven nephrotoxic effect in many reported cases, renal angiography should not be used in the diagnosis of renal disease."

Although one instinctively sympathizes with the tragedy of their reported case, it seems too great a reaction to condemn a procedure which has proved diagnostic usefulness and which has been performed many thousands of times in skilled hands without the complications they observed.[1,3,7]

From the very first, those surgeons interested in arteriography have emphasized its value in the study of vascular lesions of the aorta and its branches. It is in these areas that it has its greatest and perhaps only usefulness. Renal arterial disease and anomalies of renal vasculature, either congenital or acquired, can be viewed to great advantage by aortography.[2,6] It would seem a step backward to deprive the surgeon of the advantages of this preoperative study. Indeed, in some cases of renal arterial disease with associated hypertension, aortography is the only accurate way at present of visualizing the lesion and planning a surgical attack.[6]

From personal experience during the past nine years, I agree with the authors' conclusion that renal angiography is sometimes unreliable in differentiating between renal cysts and tumors. However, in problems involving renal arterial disease (occlusive lesions or aneurysms of the renal arteries, renal infarction, some cases of renal arterial trauma, and multiple renal arteries with ureteral obstruction) it is possible to gain valuable information about renal vasculature. The procedure also has value in preoperative evaluation of some adrenal tumors.

Hinman has emphasized the danger of large doses of contrast material injected under great pressure.[5] In many of the cases tabulated by Conger and colleagues, large amounts or multiple injections of highly concentrated urographic media were used. In their own case, 20 cc. of 70% sodium acetrizoate (Urokon sodium) was injected into a 12-year-old child, under thiopental (Pentothal) anesthesia. Their roentgenograms show evidence of some extravasation. This is comparable to a larger amount in an adult and fits in with the other cases

described in their Table. When certain precautions of technique are employed, the danger of the accidents described by the authors is lessened.

The following technique, when carefully followed, is believed to be safer than the techniques described in the cases with fatality:[4]

During heavy sedation with pentobarbital, morphine, and scopolamine, the procedure is performed under local anesthesia, with use of ample amounts of 1% procaine.

After a satisfactory tap of the aorta has been obtained and a trial injection with isotonic saline indicates that there is free flow through the needle, a small test injection of 1 or 2 cc. of contrast medium is made to determine the position of the needle and as a kind of a "scout film" to assess the situation as regards other vital structures, extravasation, or evidence of aortic occlusion.

Fifty per cent sodium iodomethamate U. S. P. (Neo-Iopax) is used as the radiopaque medium of choice. Because of several recent reported fatalities with acetrizoate, we have abandoned this material for use in aortography.

Before the test injection and before each succeeding injection, 5 to 8 cc. of 1% procaine is injected into the aorta through the translumbar needle.[5] This reduces vasospasm, decreases the transient pain that the patient has under local anesthesia, and, I believe, is an important factor in preventing the type of vascular damage observed by Conger and his colleagues.

The scout film made with the test injection is viewed and carefully studied before a final injection is made. If there is any question of improper position of the needle or other possible complication, the procedure is terminated or else the needle is withdrawn and reinserted at a different level.

The final injection for diagnostic purposes is made with no more than 12 cc. of the contrast medium injected by a 10 cc. hand syringe using manual pressure. This small amount of 50% medium injected by hand eliminates the danger of excess pressures and large volumes. The pictures obtained are usually satisfactory. In children, because of the smaller aorta and other vessels and the smaller vascular pool, the quantities of dye injected are proportionately less.[6] Occasionally, under special circumstances, a second full injection of 10 to 12 cc. is made for better visualization, but this should never be done if the needle is found to be in a dangerous position or if there is evidence of extravasation or aortic obstruction.

Following the last injection of opaque material, a further intra-aortic injection of 5 cc. of 1% procaine is introduced, followed by 20 to 25 cc. of isotonic saline.

The compelling arguments of the excellent paper by Conger, Reardon, and Arey cannot be ignored. However, the lesson is not that the procedure is totally bad; rather it is that the procedure may be dangerous when relatively large amounts of too highly concentrated urographic media are injected without regard for their effect on the renal arteries.

Translumbar and/or percutaneous femoral aortography are useful adjuncts to other diagnostic procedures in cases where visualization of the renal arteries is important. Aortography continues to have a useful place when properly performed in selected cases.

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Announcements

Seventh International Cancer Congress.—The Seventh International Cancer Congress will be held in London, England, July 6-12, 1958, under the presidency of Sir Stanford Cade. Congress headquarters will be The Royal Festival Hall.

There will be two main sessions of the Congress: (a) Experimental and (b) Clinical and Cancer Control.

Special emphasis will be placed on hormones and cancer, chemotherapy, carcinogenesis, and cancer of the lung.

Proferred papers will only be considered if submitted with an accompanying abstract (not over 200 words) before October, 1957, and if dealing with new and unpublished work.

The registration fee for the Congress will be £10 or $30 and the latest date for registration without late fee will be Jan. 1, 1958.

Registration forms and a preliminary program will be available early in 1957 on application to The Secretary General, Seventh International Cancer Congress, 45 Lincoln's Inn Fields, London, W. C. 2, England; J. H. Maisin, President, Union Internationale Contre Le Cancer, Voer des Capucins, 61, Louvain, Belgium, or Harold Dorn, Secretary General, Union Internationale Contre Le Cancer, National Institute of Health, Bethesda 14, Md., U. S. A.

Surgery Illustrated

Technique of Pneumonectomy

ALTON OCHSNER, M.D., New Orleans

The extirpation of an entire lung may be performed either for neoplastic disease or for inflammatory processes. Although in each instance the entire lung is removed, the technique of removal varies. When a lung is removed for neoplastic disease, it is necessary to perform a much more radical procedure in that an en bloc excision of the mediastinal lymph nodes is also included, whereas in a pneumonectomy for inflammatory disease it is generally not necessary to remove the mediastinal nodes.

A pneumonectomy is an anatomic procedure generally, because, unless there is considerable involvement of the mediastinum, the dissection, which is done entirely within the mediastinum, is performed at some distance from the disease process. Unfortunately, however, the disease process, whether it is neoplastic or inflammatory, frequently extends to involve the mediastinum, and in such instances mediastinal dissection is much more difficult.

As previously emphasized, in cases in which it is known that pneumonectomy is the desired procedure, I prefer an anterior approach rather than a posterior lateral one, which is used by most surgeons. An anterior approach facilitates the procedure for both the anesthesiologist and the surgeon, because with the patient in the supine position there is less circulatory and respiratory interference and also because the distance from the anterior chest wall to the mediastinum is actually shorter than the distance from the lateral chest wall to the mediastinum. As a result of gravity, this latter distance is increased by the sagging of the mediastinum away from the chest wall with the patient in the lateral decubitus position. In many cases with neoplastic disease, however, it is not possible to make a definite diagnosis preoperatively, and an exploratory thoracotomy is done. Because of the possibility that the lesion in such a case may be inflammatory, in which instance a lobectomy may be performed rather than a pneumonectomy, it is our custom to use a posterior lateral incision when the diagnosis of malignant disease has not been confirmed preoperatively, because a lobectomy is difficult to perform through an anterior incision.

Submitted for publication Oct. 18, 1956.

From the Ochsner Clinic and the Ochsner Foundation Hospital.

Technique of Pneumonectomy: Anterior Approach

The patient is in the supine position, but with either the table slightly tilted away from the surgeon or the patient tilted on the table by placing sandbags beneath the shoulder and hip on the side to be operated upon and with the arm of the patient on the side to be operated upon in an abducted position on an arm board or supported from a frame connected to the operating table (Fig. 1*A*). The tilting of the table away from the surgeon is desirable in order to facilitate manipulations of the assistants, who otherwise would have to reach over the shelving edge of the sternum, which is extremely uncomfortable. A transverse incision is made in the third intercostal space beginning at the midportion of the sternum and extending laterally to the midaxillary line. The incision extends through the skin, subcutaneous fat, and pectoralis major and minor muscles, and the intercostal muscles in the third intercostal space are exposed.

Immediately above the fourth rib the intercostal muscles are divided fairly far laterally in the incision. The incision is then extended laterally to the midaxillary line and medially to within about 4 cm. of the sternum. Care is taken not to injure the internal mammary vessels. The third and fourth costal cartilages are divided close to the sternum after separating the perichondrium; the medial portion of the costal cartilage is then removed by means of a rongeur. Transfixion sutures of crochet cotton No. 20 are inserted around the internal mammary vessels above and below the proposed division of the vessels (Fig. 1*C*). Following the tying of these sutures, the intercostal muscles medially, including the internal mammary vessels, are divided. There is usually very little bleeding from the internal mammary vessels because of the previously placed transfixion sutures. Following their division, the internal mammary vessels are individually clamped and ligated with quilting cotton ligature.

The ribs are separated by means of a Finochietto rib spreader, care being taken not to separate the ribs too rapidly because of the danger of breaking them. This is particularly true in older persons. It is surprising, however, how wide a separation can be obtained if sufficient time is elapsed for the chest wall to give. After sufficient separation of the ribs to secure adequate exposure of the lung and hilum, the lung is carefully examined and any adhesions between the lung and parietes are divided. A longitudinal incision is made in the mediastinal pleura, preferably posterior to the phrenic nerve (Fig. 2*A*). This is extended superiorly to the apex of the pleural cavity. The vena azygos major vein is isolated, doubly ligated, doubly transfixed, and divided (Fig. 2*B*). Following this, it is possible, after determining whether the lesion is operable, to free en bloc all the nodes in the superior mediastinum and to dissect them from the apex of the pleural cavity downward toward the hilum (Fig. 3).

The mediastinal dissection is then begun. The first assistant retracts the mediastinum medially with a sponge on a holder, and the superior vena cava is mobilized medially (Fig. 2*A*). This is done partly by sharp and partly by blunt dissection, the latter being accomplished by means of small pledgets of gauze on curved forceps (dissectors). The pulmonary artery is freed well into the mediastinum, and by means of a Semb ligature carrier a crochet cotton ligature, No. 10 or 20, is inserted around the vessel and tied distally (on the lung side) (Fig. 2*C* and Fig. 4*A*). Another crochet cotton ligature is placed around the pulmonary artery. While the first assistant retracts the superior vena cava with a sponge on a holder with one hand, he holds the ligature taut, and the operator, with his index finger of the left hand posterior to the artery and the thumb anteriorly, "walks" the ligature into the mediastinum by alternately taking one side of the ligature and then the other with a long thumb forceps and moving it medially (Fig. 4*B*). During this procedure the ligature is kept taut. After the ligature is sufficiently far medially, the operator maintains it in position by keeping the index finger on the posterior part of the vessel and the thumb anteriorly, this being maintained while the first assistant ties the ligature (Fig. 4*C*). During the latter maneuver, the operator retracts the vena cava by means of a Semb ligature carrier. Because of the size of the vessel, it is necessary to allow sufficient time for the ligature to seat itself. After this ligature has been tied, two transfixion sutures are introduced, one which enters the vessel from the inferior aspect and comes out superiorly and another which enters the vessel anteriorly and courses posteriorly (Fig. 5). Each of these ligatures is tied anteriorly, and then one end of the transfixion suture is pulled around the vessel and tied again. In this way, four quadrants of the vessel are caught. Finally, a transfixion suture is placed laterally, immediately adjacent to the lateral ligature, and before the pulmonary vessel is divided an Ochsner

clamp is placed on the lateral aspect of the artery. The artery is divided immediately adjacent to and medial to the clamp (Fig. 5*C*). This gives a sufficiently long stump of the vessel so that there is no danger of the ligatures slipping.

The pulmonary veins are similarly treated. It is frequently necessary to ligate the pulmonary vessels within the pericardium. Generally, the pulmonary veins are ligated as separate structures, but occasionally, if the lesion extends medially, it is necessary to ligate the pulmonary veins as a common trunk, particularly on the medial aspect. Not infrequently, because of the extent of the tumor medially, it is necessary actually to place the ligature and the transfixion sutures through the auricle. The inferior pulmonary ligament is divided and the mediastinal pleura inferiorly is opened. The lymph nodes in the inferior portion of the mediastinum are freed, beginning inferiorly and extending up toward the hilum. The pleural reflection posterior to the hilum is incised; all the nodes in the mediastinum are dissected upward toward the carina and dissected away from the carina and the bronchi. The bifurcation of the trachea is carefully dissected free of lymph nodes; the bronchial arteries are identified, clamped, divided, and ligated, and then two bronchial clamps are placed obliquely across the bronchus so that immediately adjacent to the trachea all of the bronchus is removed (Fig. 2*F*). The bronchus is divided between the two clamps, and the lung is removed. In cases in which the lesion extends up to the trachea, bronchial clamps are not employed, and it may be necessary to include a portion of the trachea in the resection. The bronchial stump is closed by introducing crochet cotton sutures on French eye needles proximal to the clamp, one at either end, which are tied. A series of similar sutures is placed proximal to the clamp, but they are not tied until all the sutures have been introduced (Fig. 6*A*). The clamp is removed and the individual sutures are tied, care being taken not to tie the sutures too tightly, because they can cut through the bronchial wall (Fig. 6*A*). After completion of the bronchial suture, saline solution is placed in the pleural cavity and the anesthesiologist applies pressure to his bag to increase intratracheal and bronchial pressures. If there is escape of air from the end of the bronchus, the bronchial closure is inadequate and more sutures are inserted.

It is extremely desirable to cover the bronchus with pleura. If it has not been necessary to dissect away too much of the mediastinal pleura, this can be easily accomplished by the approximation of the anterior and posterior leaves of pleura over the bronchial stump. If, however, because of extensive involvement of the mediastinal pleura it has been necessary to remove a great deal of the pleura, closure usually can be accomplished by shifting a pedicle of mediastinum to cover the bronchial stump adequately (Fig. 6*C*).

The ribs are approximated with a rib approximator. Although we previously employed pericostal sutures after approximating the third and fourth ribs, we now drill several holes in the adjacent ribs and, through these, insert stainless steel wire sutures, which when tied maintain approximation of the ribs without pressure on the intercostal structures (Fig. 6*D*). The pectoral muscles and fascia are carefully sutured. A small catheter is placed in the wound anteriorly, which is left in until the wound is completely closed and until the patient is removed from the tilted position. Before the tube is removed, the opposite lung is expanded; this allows the mediastinum to shift back to its normal position, and the tube is then removed. A compression bandage is applied to the wound.

Technique of Pneumonectomy: Posterior Lateral Approach

The patient is in the lateral decubitus position, lying on the unaffected side. He is held in this position by adhesive straps, which are placed over the hips and shoulders to keep him from turning. The incision be-

gins anteriorly in the region of the fifth rib, courses posteriorly, curves around the angle of the scalpula, and courses superiorly paravertebrally (Fig. 7). The incision extends through the skin, subcutaneous fascia, and serratus and latissimus dorsi muscles. The scapula is elevated and the fifth rib identified. The fifth rib is removed subperiosteally through its extent from its posterior extremity, which is exposed by retracting the quadratus lumborum muscle medially. After removal of the fifth rib, the pleura is opened throughout the extent of the incision and careful exploration of the pleura cavity is performed. Any adhesions that are present are divided by sharp dissection, and the rib edges are separated by means of a Finochietto retractor with a long blade superiorly so as to include the angle of the scapula and the fourth rib and the short blade inferiorly. The rib spreader should be opened slowly so as to get sufficient exposure and not to break a rib. The pneumonectomy is performed in virtually the same manner as when the anterior approach is employed (Fig. 7). It is somewhat easier to remove the nodes in the superior and inferior mediastinum through this approach than through the anterior approach. However, the advantage of having the patient in the supine position and the ease with which the patient can be handled certainly offsets the greater difficulty in dissecting the superior and inferior mediastinal nodes.

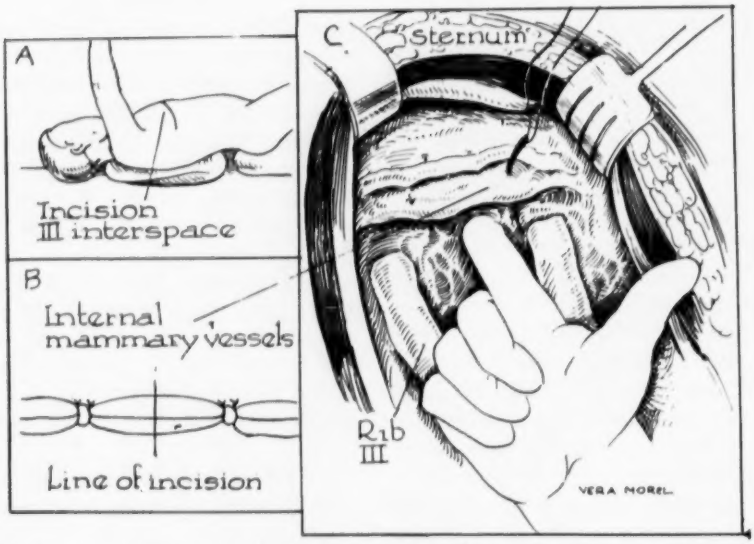


Fig. 1.—For all patients in whom a diagnosis of carcinoma of the lung is made preoperatively, the anterior approach is used. The hips and shoulders on the side to be operated upon are elevated by placing sandbags beneath them. A transverse incision is made in the third intercostal space, and after skin, fascia, and pectoralis major intercostal muscles laterally are divided a transfixion suture is placed around the internal mammary vessels before they are divided. After ligation of the internal mammary vessels, they are divided as shown in *B*.

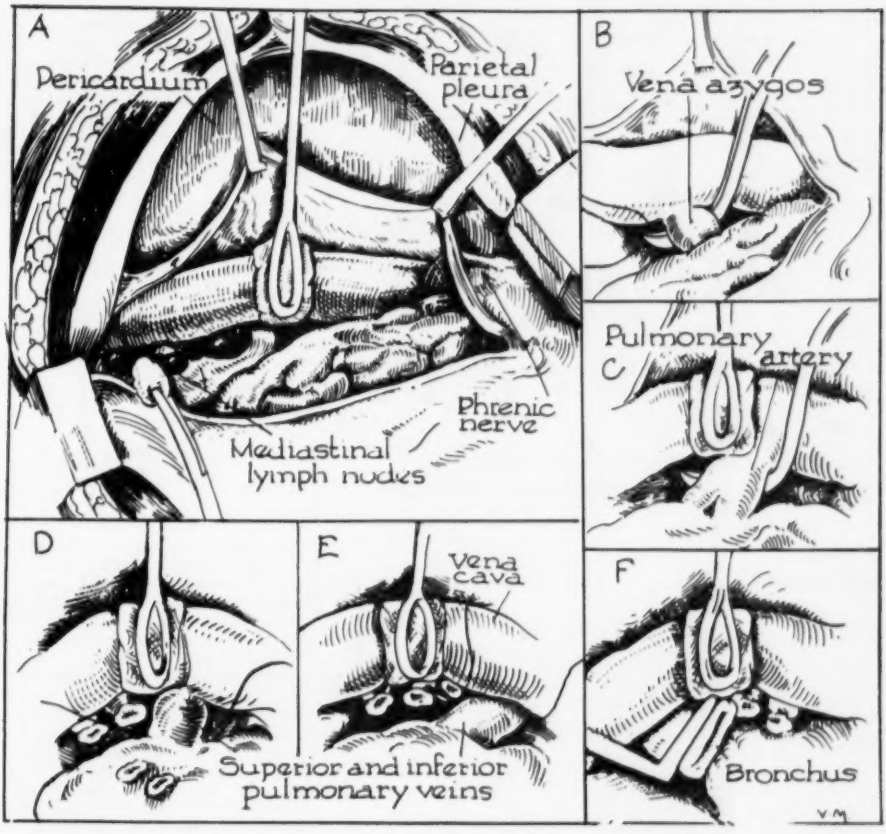


Fig. 2.—After the chest is opened, the adjacent ribs are separated by means of a Finochietto retractor. A longitudinal incision is made in the mediastinal pleura posterior to the phrenic nerve. As shown in *A*, this incision extends up to the superior aspect of the thoracic cage and an en bloc excision of the lymph nodes, beginning above, is done. All the nodes in the superior mediastinum are dissected downward. The vena azygos major on the right side is ligated medially and distally and transfixed medially and distally as shown in *B*. Following this, the pulmonary hilar vessels are individually treated, usually beginning first with the pulmonary artery, following which the two veins, the superior and inferior pulmonary veins, are individually ligated, transfixed, and divided. Finally, the bronchus is divided between clamps.

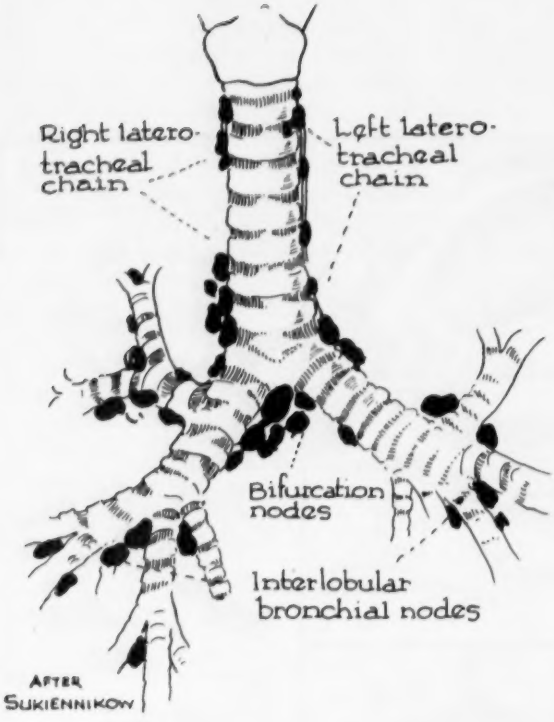
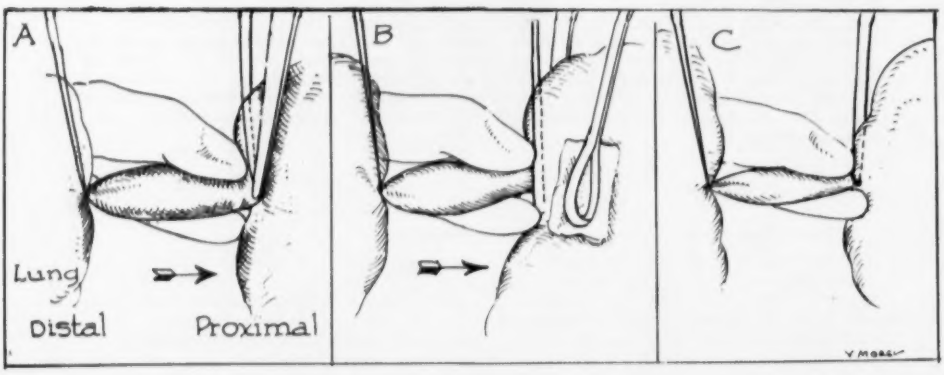


Fig. 3.—Diagram showing the principal lymph nodes of the tracheobronchial tree. It is extremely important that all of these should be removed, including those that extend up to the superior portion of the thorax, down along the trachea, and inferiorly as well.

Fig. 4.—Technique of ligation of the hilar vessels. After placing a ligature around the vessel, the ligature is tied distally. Following this, the proximal ligature is "walked" into the mediastinum. The assistant holds the ligature tautly while the surgeon places the index finger of the left hand behind the vessel and the thumb in front of it. By means of long tissue forceps the vessel is "walked" into the mediastinum by first advancing it on one side and then on the other, during which maneuver the finger and thumb follow closely and maintain the ligature in the medial position while the assistant ties it.



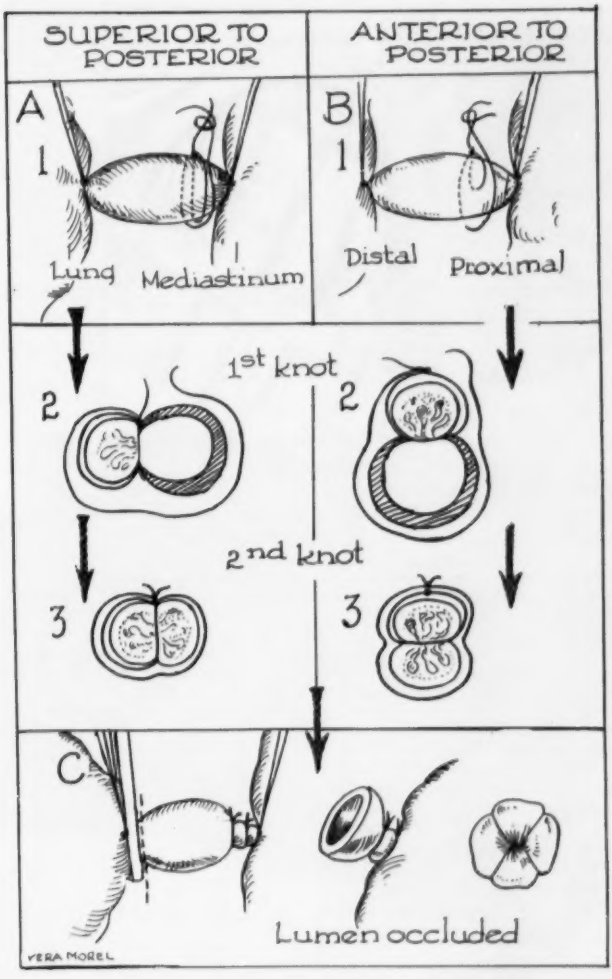


Fig. 5.—Method of insertion of transfixion sutures in the pulmonary vessel. Two transfixion sutures are placed on the cardiac side and one on the pulmonary side. They are placed in such a way that four quadrants of the vessel are secured. As shown in *A*, the first suture begins anteriorly and extends posteriorly. This is then tied, and the end is brought around and tied on the opposite side. The second suture begins inferiorly and courses superiorly. This is tied and then brought around. A cross section of the method of insertion of the suture is shown in A2. Following completion of the two sutures proximally, a single transfixion suture is placed distally, and following this a hemostat is placed immediately adjacent to the lung and the vessel is divided immediately adjacent to the clamp, which permits the leaving of a long stump on the cardiac side.

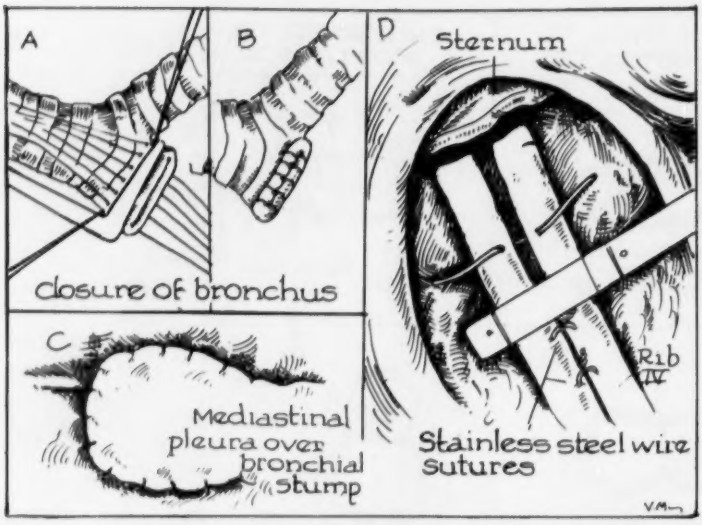


Fig. 6.—Technique of bronchial closure. Two right angle clamps are applied to the bronchus, the proximal one at the very beginning of the bronchus, the distal one immediately distal to this. The bronchus is divided between two clamps, and a suture is then placed at either end of the bronchus and tied. After this maneuver, a series of sutures is placed proximal to the clamp, but they are not tied until the clamp is removed. After insertion of the sutures, the clamp is removed and the sutures are tied. Following closure of the bronchus, normal saline solution is poured into the chest and intrabronchial pressure is increased by the anesthesiologist to determine whether there are any leaks. The bronchial stump is then covered with pleura, either by approximating the adjacent edges or by the formation of a flap as shown in *C*. The chest is closed by drilling holes into the adjacent ribs, and, after the ribs are brought together with a rib approximator, crochet cotton or steel wire sutures are introduced through the previously drilled holes, and the ribs are sutured.

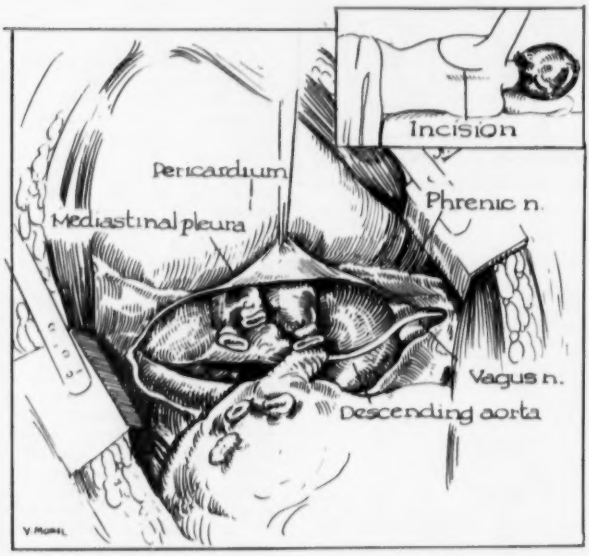


Fig. 7.—In cases in which a positive diagnosis has not been made, a posterior lateral incision is made extending paravertebrally around the angle of the scapula anteriorly over the fifth rib. The fifth rib is resected and the operative procedure is the same as that illustrated in the previous Figures.

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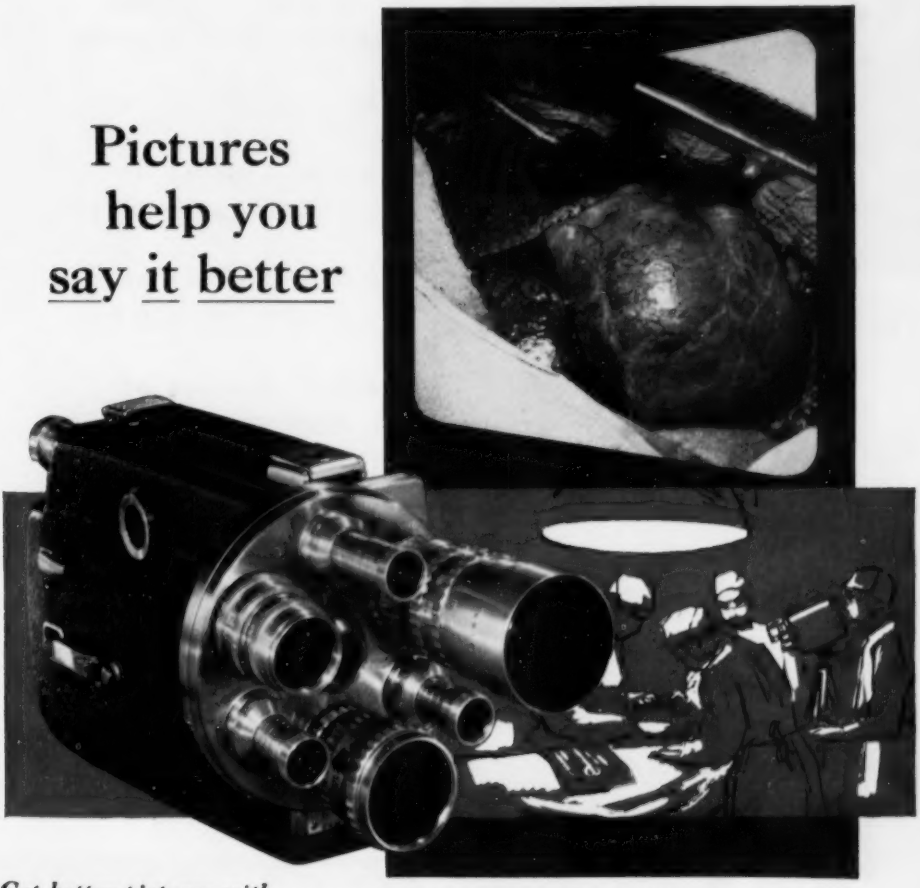

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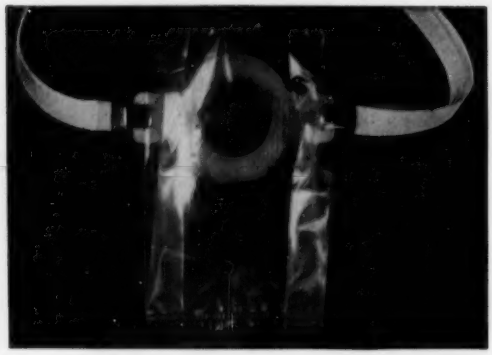

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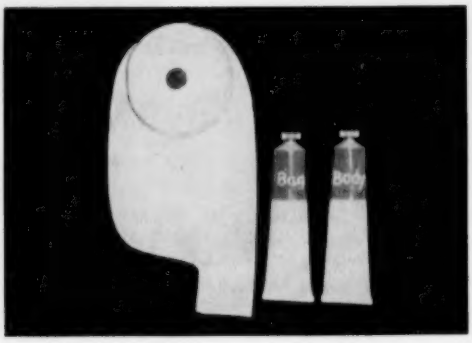

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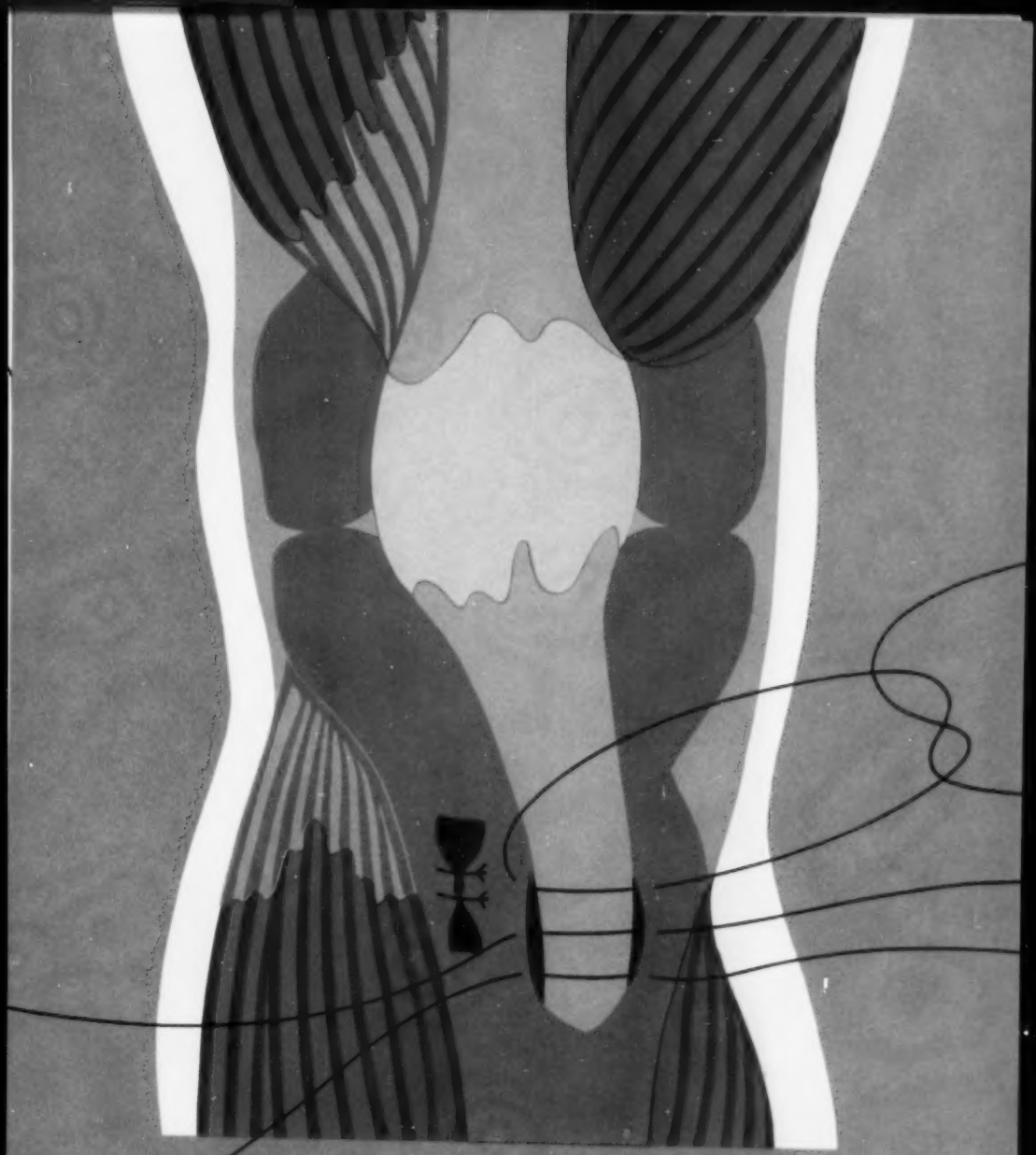

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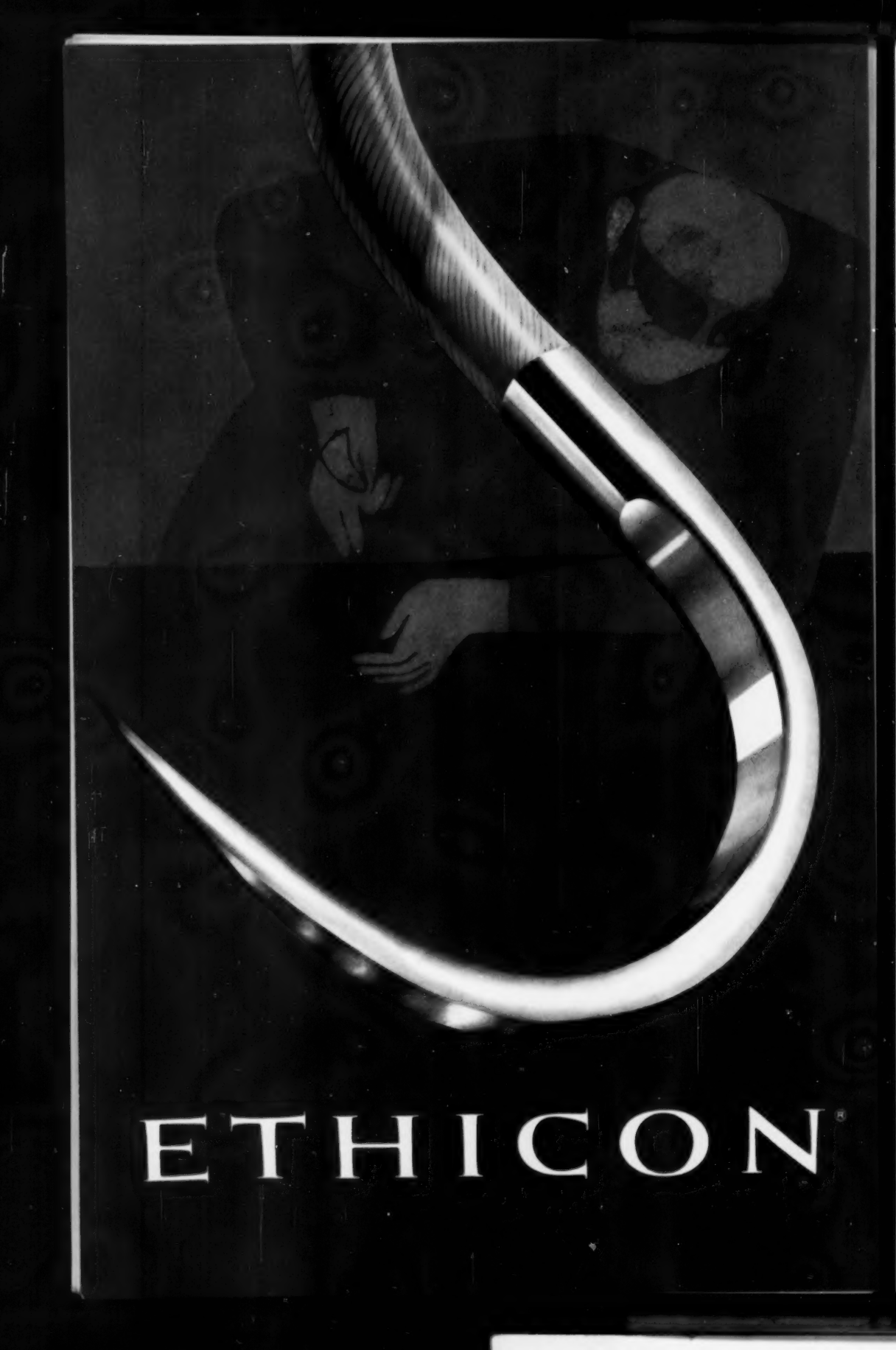
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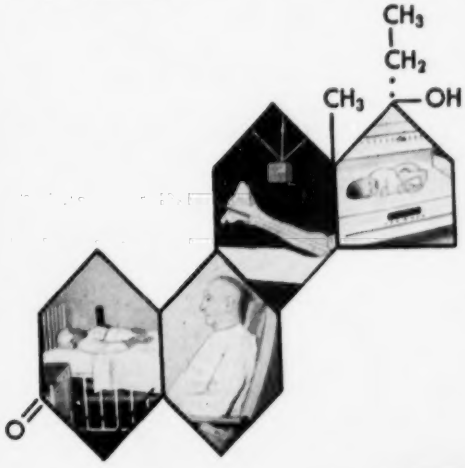

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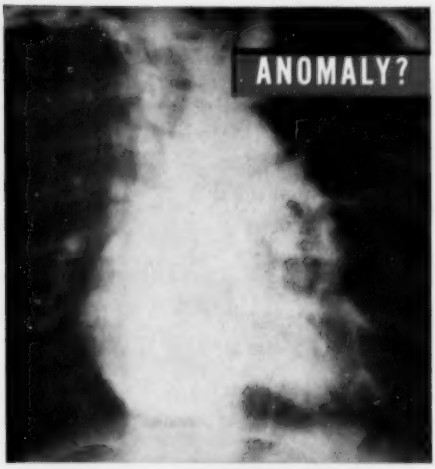

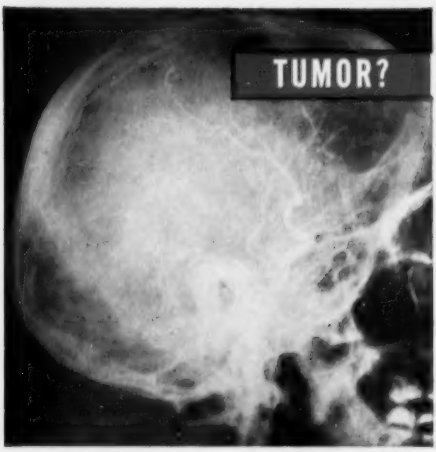

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